WORLD HEALTH ORGANIZATION

Ethics, access and safety in tissue and organ transplantation: Issues of global concern

Madrid, Spain, 6-9 October 2003

Report

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Introductory Note from the Secretariat

This publication provides an account of the points discussed and the conclusions reached at a consultation on the ethical, access, and safety issues in tissue and organ transplantation held by the World Health Organization (WHO) in Madrid on 6-9 October 2003. A consultative process was carried out jointly by the Department of Ethics, Trade, Human Rights and Health Law (ETH) and the Department of Essential Health Technologies (EHT) in response to the request of WHO's Executive Board at its 112th session in May 2003 that the Director-General examine this field, including both human-to-human and animal-to-human transplants. This consultative process culminated in the Madrid meeting.

Planning for the Madrid meeting was facilitated by scientific advice from the transplant authorities in France, Spain and the United States of America, among others. The consultation was sponsored by the Ministry of Health of Spain, with additional financial support from the US Department of Health and Human Services (through the Pan American Health Organization/WHO Regional Office for the Americas). We gratefully acknowledge this aid, and in particular we wish to thank the staff of the Organizacion Nacional de Transplantes for their efficient assistance in preparing and supporting the consultation.

This report represents the views of the consultants, not necessarily those of WHO. It has, however, been indispensable in the Secretariat's preparation of a report for the January 2004 session of the WHO Executive Board (Document EB113/14). The present report was prepared by the undersigned, with the efficient administrative and secretarial support of Chris Faivre-Pierret; it is based on a draft written by the meeting's two Rapporteurs, Drs Farhat Moazam and Jeremy Chapman, whose scientific and ethical expertise, remarkable ability to summarize complex materials succinctly and commendable alacrity are gratefully acknowledged.

All the 37 clinicians, ethicists, social scientists and government officials from 23 countries at the consultation were active and helpful participants in the meeting and we thank them all for their individual and collective advice. The Secretariat owes a special debt to meeting's Chair, Dr Carl-Gustav Groth, and co-Chair, Dr Blanca Miranda, for their invaluable contributions both during and after the meeting.

The report was submitted to all participants for comments. We are grateful to them for their helpful comments. Any errors or omissions are, of course, our responsibility, not theirs.

A.M. Capron, Director, ETH/SDE
L. Noël, Project Leader, EHT/HTP
N. Biller-Andorno, Ethicist, ETH/SDE

Executive Summary

Transplantation of organs, cells and tissues are now effective therapies across a wide range of both fatal and non-fatal diseases. The excellent survival and success rates of transplantation of organs and cells, such as the kidney, liver and heart or haematopoietic stem cells in immunosuppressed patients, have led to high levels of demand globally. The success rates for transplantation of certain cells or tissues which do not require immunosuppression have also ensured that such procedures are frequently the treatment of choice in the respective therapeutic areas. It is, however, clear that ethically-unacceptable practices occur in a number of countries.

Neither measurements of activity in, nor outcome of, organ, tissue and cell transplantation is available globally. There are data from countries with compulsory registration of transplant activity and there are voluntary registries of some types of transplantation.

Despite the appropriate focus on prevention of disease, the global needs of patients for transplantation are not being met. The demand has outstripped the supply of organs, cells and tissues from both deceased donors and from the altruistic living relatives of patients in need. The alternative treatments and medical support for patients with end stage organ failure, especially renal dialysis, are expensive and limited in many countries. There is also a lack of clinical expertise in some regions and countries and an inability to fund transplantation to some extent in all countries. Thus in all Member States one or more influences prevent the sufficient supply of transplantation therapies and lead to pressure for non-altruistic living donation.

Deceased donation is meeting the needs of transplantation in few, if any, countries. Potential donors are reluctant to commit to donate after death and their families may refuse permission when approached after death. The use of executed prisoners as organ donors in some countries causes great concern that these donations are coerced. Member States employ different models of consent including: presumed consent or “opt out”; required requesting; “opt-in”; and mixtures of these three models. Independently from which specific model is chosen, information and voluntariness are of fundamental importance for the act of post-mortem donation.

Increasing use, over the past ten years, of living donation of non-regenerative organs has extended from kidneys to livers and even to the lung and pancreas in some instances, despite the hope that reliance on living donors could be reduced. There remains great concern that a market in body parts (especially the kidney) has flourished over the past few years with vulnerable persons being tricked or coerced into donating and some recipients travelling with their surgeons to countries where "donated organs may be purchased legally or illegally.

Human cells, human tissues and human organs provide different concerns. Tissues are processed and traded in many Member States by both for-profit and not-for-profit organizations. It is not clear the extent to which donors or their families are aware of the

profit that is created through this trade. Human cells, in particular haematopoietic stem cells, on the other hand, are widely and increasingly exchanged globally between donors and patients through arrangements made by not-for profit organizations which isolate and protect the anonymity of both patient and donor.

Xenotransplantation represents a potential opportunity to ensure a constant supply of organs and tissues for transplantation. However, the scientific hurdles to successful xenotransplantation in humans currently mean that it should only be undertaken under strict clinical trial conditions. There are substantial potential risks to human health from the transmission of xenogeneic infectious agents through xenotransplantation. Careful international monitoring of these clinical trials and of each subject is thus essential to ensuring the safety not only of subjects but also of their families and the broader human population. These issues transcend currently accepted norms of subject consent and medical responsibility for monitoring of the consequences of xenotransplantation.

It is clear that some Member States have not assumed or have been unable to assume an appropriate level of responsibility in each of the areas of transplantation. There are a number of roles for which the World Health Organization is best placed to ensure that minimum levels of human access, safety and ethical practice are adopted universally.

WHO roles could include:

(1) Encouraging the development of transplantation therapies in Member States in an ethically appropriate manner.

(2) Initiating an ongoing programme on transplantation at WHO and establishing a WHO Expert Advisory Panel for transplantation.

(3) Facilitating the development of a core of technical and ethical standards for the management of the safety, quality and efficacy of human material for transplantation that can serve as a model for Member States.

(4) Encouraging Member States to develop a legal framework and national policy and plan on transplantation activities, especially ensuring coordination of the procurement of human material from deceased donors.

(5) Facilitating communication between regulators and providers on the international circulation of human cells and tissues for transplantation, in particular for matched haematopoietic stem cells.

(6) Collecting data on the extent of paid organ, cell and tissue donation.

(7) Creating a global map of the known infectious risks and the safety measures that are applied to donors and donations in different countries and regions of the world.

(8) Helping Member States to develop capacity for national regulatory approaches to quality and safety in particular by encouraging the creation of international support networks.

(9) Encouraging the measurement of the donor outcomes for living donors in different clinical environments, through collaborative global data collections.

(10) Encouraging nations to support consensus on basic principles of xenotransplantation safety and oversight:

- Defining the nomenclature of different types of xenotransplantation.
- Identifying countries in which xenotransplantation occurs.
- Supporting the approach that regulation must be in place in all countries in which clinical trials of xenotransplantation occur.
- Developing general recommendations for obtaining informed consent in situations that may represent a risk to the general public and in which individual rights and the public good may come into conflict.
- Fostering agreement between Member States to control travel for the purposes of xenotransplantation.
- Implementing an international xenotransplant surveillance system.

(11) Rewriting and updating the Guiding Principles, published by WHO in 1991, especially concerning:

- Measures to ensure safe and voluntary altruistic donations from living donors.
- Financial transactions and coercion.

Opening session

Dr Blanca Miranda welcomed delegates and introduced Dr Perez Santamarina, the General Secretary of Health, who welcomed delegates on behalf of the Spanish Ministry of Health. He emphasized that the respect of human rights must govern all actions in the field of transplantation medicine and that basic standards need to be established to control research, indications, allocation rules, and any other area where ethical principles can be violated. He welcomed WHO's renewed interest in transplantation medicine and pledged that the Spanish Department of Health would cooperate with this initiative.

On behalf of WHO, Alex Capron thanked the Government of Spain for hosting the meeting, the Organizacion Nacional des Transplantes for their organizational and scientific support, the Department of Health and Human Services of the USA for contributing to funding the meeting, and the Etablissement Français des Greffes for participatint in the scientific preparation. Mr Capron welcomed the participants on behalf of the organizers and asked the participants to introduce themselves and to provide brief backgrounds.

Dr Carl-Gustav Groth from the Karolinska Institute was elected Chairperson of the meeting, Dr Miranda co-Chairperson, and Dr Jeremy Chapman from Australia and Dr Farhat Moazam from Pakistan as Rapporteurs.

Session 1 – Introduction and general objectives of conference

WHO and transplantation – Dr Luc Noël

Dr Noël provided an overview of the history and organizational structure of WHO and composition and responsibilities of the World Health Assembly (WHA) and the Executive Board (EB). He described the WHO Department of Essential Health Technologies (HTP/EHT) where the transplantation project is located. Core functions of WHO include articulation of consistent, ethical and evidence-based policies and positions, stimulating research and development, helping build sustainable national capacity, setting and pursuing the implementation of norms and standards and negotiating and sustaining global partnerships.

WHO's involvement in transplantation has been defined through WHA Resolutions (40.13 – 1987, 40.0 – 1989, 44.25 – 1991) and the 1991 Guiding Principles for Transplantation. Two Task Force meetings in 1996 and 1997 noted that transplantation, with its complex scientific as well as social, cultural and ethical aspects, was "becoming a public health issue" requiring attention by WHO. In May 2003 a background paper entitled "Human Organ and Tissue Transplantation" was submitted to the 112th session of the Executive Board for review. The Executive Board decided to set up an international group of experts to examine issues in transplantation, including xenotransplantation. This group would work with the Secretariat to prepare a report for the Board and offer recommendations for action in a report to the 113th session of the EB in January 2004.

There is "a new momentum" for involvement of WHO in transplantation with the aim of proposing a way forward for:

(1) procurement of human material for transplantation with related ethical, legal, technical and systems issues, and
(2) quality and safety of human and animal material for transplantation, including cell and tissue banking, as well as traceability and vigilance.

Objectives of meeting and method of work – Dr Nikola Biller-Andorno

Delegates were asked to focus on "realistic aims" in the meeting and to consider the ensuing report as "exploratory" rather than final in nature, the objectives of the meeting being to:

(1) map current issues in transplantation;
(2) distinguish between areas of broad consensus and areas of controversy;
(3) develop recommendations for the role of WHO; and
(4) outline desirable outcome parameters from WHO involvement.

She explained that the process of the meeting includes ensuring the maximum output from participants via discussions, presentations providing an overview of issues involving organ, tissue and cell transplantation and a series of brief presentations by participants dealing with their experiences in their countries.

Session 2 – Global activity and development in transplantation

Global activity and developments in organ transplantation – Dr Carl-Gustav Groth

Dr Groth provided an overview of the status of solid organ (kidney, liver, heart) transplantation activity from 1988-2001, comparing trends in Europe, the USA and Asia, as far as the existing data permit. There has been a steady progression in all three regions in kidney transplantation, with the frequency in Asia rapidly increasing. In 2000 alone, close to 15 000 renal transplants were carried out in each region. A similar increase in liver transplants is evident in Europe and the USA, with Asia still lagging behind. Heart transplants have shown no real increase. There is a "disquieting discrepancy" in rates of transplants between the regions. the USA carries out twice as many transplants as Europe, and Asia, with its largest population, reveals the lowest rates and greatest diversity reflecting the various levels of development and competing health priorities (annual number of kidney transplantations per million population (pmp) in the USA 52, Europe 27, Asia 3).

There has been a progressive rise in live donors in Europe and the USA, with the number of living donors actually overtaking the number of deceased donors in 2001 for the first time in the USA. Although Asia continues to have a predominance of live organ donors, here too discrepancies can be found among countries. In India and Japan kidneys and livers are almost exclusively from live donors, whereas in some other countries these organs are usually obtained from cadavers, in some cases a large number reputed to be from executed prisoners. The reasons for these discrepancies, both in the number of transplants per million population and the sources of organs, appear to be complex including indigenous cultural resistance to cadaveric donation, local health policies, lack of intensive care units, relevant infrastructure and staff to establish cadaveric programmes.

Dr Groth ended by noting that "transplantation works well" and that it should be "a common goal to make organ transplantation available as a patient service, globally". The future depends on what we do today and there is a need for global partnerships between stakeholders such as transplantation associations, industry and national and international government agencies such as WHO.

Overview of tissue banking and transplantation – Dr Rüdiger von Versen

An overview of tissue banks was provided for tissues as diverse as bone, eyes, heart valves, tendons, fascia, dura, sperm, etc. It is estimated that about 3-5 million tissue transplants take place every year globally with the highest demand in the USA, though there are only poor data on the actual levels of activity. The majority of transplants involve musculoskeletal tissues. Similar to solid organ transplants, although regional differences exist, there is a growing global problem of demand and need exceeding available supply. Several problems exist in banking and transplanting tissues. There is currently "no global uniformity and agreement on the definition of tissue". Also, despite the potential for the transfer of infections through allografts, national laws for quality and safety are either absent or in different stages of evolution in most countries including Europe and the USA. In some countries such as Germany, banks are not-for-profit ventures, whereas in others these are often profit making enterprises. There is need for standardization of the current diversity in definitions, quality and safety practices, harmonizing of national laws for tissue banking and transplantation and global networking and cooperation.

Overview of cell transplantation – Dr Jeremy Chapman

Dr Chapman provided data since 1989 that reveal a progressive global increase in haematopoietic stem cell transplantation. In many high risk haematological diseases, such as acute leukaemias and severe thalassaemias, this now provides the best and sometimes the only modality for therapy. By 2003, an estimated 8.5 million people had registered as willing unrelated volunteer donors in worldwide registries; there has been a progressive increase in the complexity and number of patients treated through international exchange of stem cells, with 1597 treated across international borders in 2001.

Challenges facing cell transplantation include improving patient survival rates, donor safety, improving the international exchange of haematopoietic stem cells and improving techniques in histocompatibility. Obstacles include ethnic diversity, costs and obstacles to cross-boundary exchanges of haematopoietic stem cells. To overcome these obstacles requires "global cooperation at all levels", "networking" and, above all, "communication".

Overview of xenotransplantation – Dr Eda Bloom

Dr Bloom presented an overview of xenotransplantation, its risks and benefits and an account of the current regulatory mechanisms in the USA. There is a global interest in research and development of xenotransplantation due to persistent and growing disparity between needs for allotransplants and available supply. One of the greatest public health concerns for clinical xenotransplantation is the risk of transmission of known or as yet unrecognized xenogeneic infections, with the concern that spread of such agents may be very difficult to contain. Evidence has shown that there have been instances of several

human pandemics in the past arising from cross-species viral infections. The risk for viral activation and transmission from xenotransplantation recipients may be greater because recipients may be immunosuppressed to inhibit immunologic rejection. In addition to the public health concerns, risks to the individual recipients include rejection and the possibility of infections in both the immediate and long term. The inadequacy or lack of diagnostic tools and absence of effective therapy, especially for xenogeneic infectious agents that have not yet been recognized, further compound these risks. Additional basic and clinical research is necessary both for safety and efficacy. Xenotransplantation should proceed cautiously with due oversight and surveillance. There is a role for international leadership, global networking and cooperation.

General discussion – Consensus points

Organ Transplantation:

- Transplantation is effective and should be seen as a "global patient service".
- Data from some regions and countries are missing, inadequate, non-inclusive.
- "Disquieting discrepancies" exist between regions related to transplants pmp. The reasons are unclear but are likely to be complex.
- There are discrepancies between countries and regions with respect to the source (live or deceased donor) of organs.
- Potential roles for WHO are: (1) addressing the fact that live donations are increasing globally despite the 1991 Guiding Principles; (2) facilitating better national, regional and global data; and (3) fostering qualitative research of diverse cultures for better understanding of the global discrepancies in transplantation.

Cell and Tissue Transplantation:

- The sector is rising rapidly and thus needs to be taken into account by WHO guidelines. Some components of tissue transplantation pose greater problems as they do not provide "origin to destiny" traceability.
- There is a need for uniformity, agreement, harmonization on definitions of "tissue".
- Standards for quality and safety of cellular transplants must be harmonized at global level, to sustain the global exchange programmes fundamental to matching HLA.
- WHO can provide leadership to facilitate global networking and cooperation.

Xenotransplantations:

- The health gains are potentially very significant but are balanced against the potential health risks. There is thus a need for more research, surveillance and oversight and to proceed only with great caution.
- WHO can provide leadership to facilitate global agreement on precautions, networking and cooperation.

Session 3 – Current challenges and normative issues

1991 Guiding Principles: Roots and implications – Mr Alex Capron

Mr Capron traced the history of WHO involvement with transplantation starting from 1987 and the subsequent origin and formulation of the Guiding Principles that were

submitted to the Executive Board and endorsed by the WHA in 1991 (WHA 44.25). Basic premises of the Guiding Principles included the realization that "supply has never satisfied demand" with shortages leading to commercial trafficking of organs from unrelated donors and a fear of possible human trafficking. Special concern was also expressed for minors and other vulnerable people. The three fundamental precepts of the 1991 Guiding Principles were that: (1) organs should preferably be obtained from the deceased; (2) living donors should generally be genetically related to recipients; and (3) no payment should be given or received (four out of nine principles addressed issues of payment, advertising for donors and commercialization).

The Guiding Principles have influenced national legislation and professional codes but over the last ten years many transplantation practices, social and medical, are no longer in line with the Guiding Principles. These include the increasing use of live (genetic and non-genetic) donors, unrelated donors who receive some form of payment, a wider and more complex range of safety issues, issues related to xenotransplantation and the increasing use of tissue transplantation and tissue banks that challenge the "donation" model.

The question now is whether the 1991 Guiding Principles should be affirmed, modified, expanded or discarded.

Current ethical issues in transplantation – Dr Nikola Biller-Andorno

Dr Biller-Andorno reminded the participants of the four ethical principles elucidated by Beauchamp and Childress – respect for autonomy, beneficence, non-maleficence and justice and suggested that they might provide one possible framework for phrasing ethical issues in transplantation**.** She enumerated ethical concerns that can arise in the areas of deceased and living donors as well as tissue and xenotransplants. Common to all four areas are questions of eligibility and safety of donor and recipient, use of financial and other incentives, equitable access and allocation and issues of cross-border exchanges and commercialization.

She pointed out some of the major issues that need to be addressed, keeping the 1991 Guiding Principles in mind. These include on what grounds live donation can still be considered subsidiary to cadaveric donation, continuing and more complex issues of donor and recipient safety, voluntary status of consents and how best to preserve the principle of non-commercialization.

Need for governmental oversight and role of WHO – Dr Luc Noël

Dr Noël noted that ethical practice of transplantation requires "setting barriers, defining abuses". Patient safety for both donor and recipient is essential, as is concern for public health risks that can arise. It is important that countries are committed to providing oversight of all transplant activities, with health authorities ensuring legislation, regulations and standards. He spoke of the importance of government-public partnerships and also of national, inter-country, regional and global cooperation and communications.

"Core ethical and technical principles on the basis of the 1991 Guiding Principles" are needed. These must also deal with the issue of access to transplantation, issues of quality and safety, and a rational and cost-effective use of transplantation. The role of WHO can be to facilitate the formulation of global principles, keeping in mind regional

and cultural diversity. It can recommend guidelines and facilitate their implementation. Furthermore, WHO can circulate information at a global level and also help to identify successful "models".

General discussion – Consensus points

- Several assumptions within the 1991 Guiding Principles have not been borne out by contemporary transplantation practices, thus raising the question of a need for revision of the Guiding Principles so that they can fully address current challenges.
- "Old fashioned" transplantation has expanded raising wider, more complex ethical issues that must be addressed. WHO, with its credibility and past record, is well placed to shoulder leadership.
- There was unanimous support for the need for a WHO Expert Advisory Panel for transplantation.

Session 4 – Deceased donors

The deceased donor – Dr Blanca Miranda

Dr Miranda began by providing data (year 2000) on the wide variations among different regions in the world in transplantation (kidneys and livers) using deceased donors. The deceased donors per million population ranged from 20.7 and 15.9 in the USA and Europe respectively to 1.1 in Asia and 2.6 in South America. She then gave a detailed account of the deceased organ donation programme in Spain, focusing on factors that contribute to its success in obtaining organs from brain dead persons. A total of 146 hospitals are authorized to obtain organs from patients with encephalic death. The average donor rate in each is 9.6, higher than in France and Germany. In 2001, of the total number of encephalic deaths in Spain, it was possible to obtain organs from 48.7%.

In 15.8% of cases the family refused to allow donation. Strategies to decrease refusal rates by families include efforts at education of the general population, opinion leaders and health care workers individually and through the mass media. For cadaveric donation, "society remains a crucial aspect in a transplant programme". Transplantation programmes must "focus on ethics, access and safety". It must be "a system that society can trust" in order to improve cadaveric donation.

Prior consent of deceased and family permission – Dr Diego Gracia

Dr Gracia described the many different informed consent systems in use worldwide to obtain cadaveric organs and tissues for transplantation. In all cases, either pre-mortem consent of the donor, or consent of his family following death, or some form of a combination of the two are necessary. Dr Gracia believes that, based on the indisputable success of transplantation, excellent risk/benefit ratios and the continuing shortage of organs, there is now a need to consider another variation of the informed consent system that he termed "supererogatory permission".

The underlying premise of such a consent would be that "organs of dead people are public goods", and donation must be considered "similar to other compulsory civil

obligations" within society. The permission is thus a moral rather than a legal requirement. Although this recommendation may appear to be a "radical solution" and is currently "illegal" he concluded that it may be time to initiate such a discussion.

Brief presentations

Japan's organ transplantation policy and the necessity for comparative study – Dr Tsutomu Iuchi

Dr Iuchi presented an overview of Japan's Organ Transplantation Law, passed in 1997, which includes the procedure for diagnosis of brain death and removal of organs. Despite this there is continuing public reluctance for cadaveric donation and transplantation with only 25 reported instances of heart beating cadaveric donation since the enactment of the Law. A public opinion poll reveals that 54% of respondents believe that "both donor's positive will and family's consent" is necessary. Only 27.6% believe that "only donor's positive will" is sufficient to recover organs. "Comparative studies looking at organ donation systems and public opinions among WHO Member States" are needed.

Consent of deceased donors in Latin American legislature – Dr Adelio Misseroni Raddaz

There is no uniformity in legislation dealing with deceased donors across Latin American countries. Legislation varies from requirement of permission from both donor and family, to "required consent" in order to obtain an identity card, to presumed consent. In many countries, refusal by family prevails over deceased's pre-mortem consent. A change is required in legislation to give preference to the wishes of the deceased and education campaigns to increase cadaveric organ and tissue donation.

Deceased donors, access to organs – Dr Carlos Soratti

Argentina has several programmes in place for the transplantation of kidneys, livers, hearts, lungs, bone marrow and corneas. In 2002, only 7.5% of kidneys transplanted were obtained from cadavers and there are more than 3 500 patients on the cornea waiting list. Problems include the fact that organ procurement remains a "marginal activity" in hospitals and there is a low level of information among hospital professionals about transplantation. WHO can promote regional educational strategies for hospital coordinators and health care professionals.

Paucity of cadaveric kidneys: A sociocultural issue – Dr Farhat Moazam

Pakistan has end stage renal disease estimated to be around 100 per million population (there is no central registry) but only 600-700 transplants are undertaken each year. Since 1985, all (except 16) kidneys have been obtained from live donors, many unrelated to the recipient. The rarity of cadaveric donation in Pakistan is due to complex reasons that include: (1) legal – no legislation yet for brain death or transplantation; (2) religious – although Muslim scholars from "academic" centres have stated that cadaveric donation is permissible in Islam, this is at variance with the "Islam of the masses" in which mutilation of the dead body is considered a sin; and (3) cultural – in a collectivistic, family centred society, obligations to family rather than autonomy and rights of individuals take precedence. There is cultural aversion to talking about one's death or "planning" it.

Solutions for increasing cadaveric donation must be found within cultural norms, using indigenous resources. WHO can help by: (1) fostering qualitative research to understand "non-medical" reasons for reluctance; and (2) encourage government/health organizations to provide the necessary legislation/oversight.

Decision making on organ donation in the Republic of Korea – Dr Kyu-Won Jung

The Transplantation Act was passed in 1999, but there is a persistent resistance to cadaveric donation in the Republic of Korea with only 36 cases recorded in 2002. The Act makes family consent essential for recovering cadaveric organs and family refusal can legally override pre-mortem consent by the deceased. Another difficulty is that most Koreans "do not express whether they (wish to) donate their organs after death or not". The problem remains how to increase cadaveric organ donation. Any guidelines "must reflect the national culture which thinks much of family member's will".

Deceased donors – Dr Ashok Shah

Dr Shah presented experience with corneal transplantation in 14 African countries. There is continuing resistance to cadaveric donation by the indigenous population. Kenya carried out around 200 corneal transplants per year, the highest in the region, but almost all corneas are donated by other countries such as Sri Lanka. The reasons for reluctance include religious/cultural factors, lack of trust, paucity of trained personnel, lack of general education and absence of eye banking facilities. All of these need to be remedied to increase cornea donation.

General discussion – Consensus points

Presentations revealed widespread community reluctance to donation of cadaveric organs in many countries throughout Africa, Asia and Latin America, even when appropriate legislation exists. Factors include both the technical (financial constraints, paucity of skilled staff, inadequate infrastructure) as well as important indigenous cultural and religious beliefs and values.

- Some countries still lack legislation for brain death and transplantation.
- Society trust remains a crucial aspect for a successful donation and transplant programme. Therefore programmes must focus transparently on ethics, access and safety.
- Possible roles of WHO – (1) seek ways to optimize the donation of organs, tissues and cells from deceased donors; (2) support and facilitate qualitative, empiric research to comprehend resistance to cadaveric donation and help find indigenous ways and local resources to increase donation; and (3) encourage and facilitate governments to have appropriate legislation and oversight mechanisms in place.

Session 5 – Living donors

Safety of the living donor: Informed consent – Dr Frank Delmonico

Dr Delmonico gave an overview of the status of live organ (kidneys, livers) donation, both from related and unrelated donors, in the USA. These data reveal that there are

significant divergences from the current WHO Guiding Principles driven in part by the improved clinical outcomes and in part by the shortage of deceased organ donors. The outcome of unrelated kidney donation is now seen to be effectively identical to the outcome of one haplotype-matched sibling transplants. In 2001, the number of renal transplants from live donors surpassed those from deceased donors, thus challenging the current applicability of WHO Guiding Principle 3, which identifies a preference for donation from deceased persons. In contrast to living kidney donation, living liver donation may have a reduced future role pending a broader understanding of the morbidity and mortality risks to the donor.

The mortality for live renal donors remains small (1 per 3000 transplants) but long-term risks and morbidity are beginning to be recognized. One analysis found that 0.04% of living kidney donors since the inception of the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) database have become kidney transplant candidates, some within four years of donation. Further analysis revealed "an additional 36 cases who had donated before UNOS began collecting data".

Based on concerns for donor safety, the Secretary's Advisory Committee on Organ Transplantation has recommended, alongside its focus on a rigorous process for voluntary and informed consent, the establishment of an "Independent Donor Advocate" in order "to promote and protect interests and well-being" of potential living donors. The areas in need of development and where WHO can play a role include: support for the generation and collection of global data on the outcome of live donation and transplantation through the development of a network of databases; development of a standard of informed consent for donors, guidelines for donor medical suitability; and guidance for national legislative frameworks.

Incentives and disincentives in organ donation – Dr Leo de Castro

Dr de Castro provided a perspective on the role of transplantation as a therapy for end stage organ failure in Asia. He raised a number of issues surrounding free and informed consent from living donors, together with the "difficulty of drawing a line between compensation and incentives" and assessing when the latter may constitute "undue influence". In family centred cultures, kinship systems and the question "who is my family?" assume great relevance. Special problems can arise in obtaining a truly voluntary consent within extended family systems and in instances of marriages of convenience.

Among his recommendations, de Castro emphasized continuing encouragement and support for cadaveric donation that also serves in a way "to protect living donors" and the requirement for "independent advocates" as well as "ethical committees and ombudsmen" as some of the "safety nets". He mentioned the need for establishing resource centres including national, regional and global registries to research long-term outcomes of living donors and provide data on the side effects and consequences. There is a need for clear identification of responsibilities for implementation of guidelines at various levels and an affirmation of physician responsibility over the transplant process. Private sector initiatives should be encouraged and provisions made for technical assistance for capacity building of national transplant monitoring and accreditation bodies. Mechanisms must be established to promote awareness and observance of WHO Guiding Principles and he emphasized a need for reporting by governments on their implementation.

Global justice, organ vending and trafficking – Dr Nancy Scheper-Hughes

The presentation began with Dr Scheper-Hughes' description of the primary goals of "Organ Watch" that include efforts to "map global trafficking" and "identify renegade hospitals and physicians". Data are now available supporting allegations of global traffic in human organs and tissues that suggest that there are numerous problems that need to be addressed at the global and international level. There is evidence for rapidly developing "transplant tourism" and "organ tourists" who travel to specific countries, often with their surgeons, to purchase organs. The abuses are centred around the concepts of the "invisible donor" and an "expendable population" that "internet brokers" and others exploit to serve the needs of the privileged.

Ethical concerns also involve issues of race, class and gender inequities in harvesting from donors and distribution to recipients and kidney theft during routine operations. There is evidence of use as donors of coerced prisoners, the mentally ill, the homeless and other populations at risk. Organ trafficking appears to be occurring as flagrant and direct violations of the law of many countries with a flourishing of broker nations, intermediary brokers and corporations. The consequences are not merely for individuals; trafficking also has major "social, economic, medical and political" repercussions for involved countries.

Brief presentations

The Indian scenario for renal transplantation – Dr Kanjaksha Ghosh

In India there are no national registries but it is estimated that live related donors constitute 40%-50% of cases and unrelated donors another 40%. Currently cadaveric renal transplants occur in less than 10% of patients. Dr Ghosh stated that problems that can be identified for live donors include poverty, illiteracy, use of inducements for donation and lack of safety measures and protection of donors and recipients. Legislation against paid donation has resulted in these procedures being pushed "underground." Solutions needed include public education, insurance to protect donors, registries and auditing. A stronger role for the Medical Council of India is also necessary with quality control measures and formal investigation of transplant-related deaths or disability of the donor or recipient.

Global issues in living donation – Dr Abdallah Daar

Dr Daar stated that there is a need to accept that deceased donation will never meet the needs of patients, especially in developing countries and furthermore that "condemnation of paid living donation has failed" to halt the practice "There is no moral reason for banning" paid donation. It is now important instead to address methods to minimize harm from living donation, "reduce the rampant, unregulated commerce" and the "exploitation that occurs of vendors and buyers". It is necessary to "not confuse revulsion of abuse of the practice with its moral probity". Solutions include addressing how to increase cadaveric donation and whether it is possible to develop policies to "implement ethically-acceptable payments".

General discussion – Consensus points

- In clinical practice there is currently a preference for living over deceased donation, despite the desire to maximize deceased over living donation.

- Local regulation and enforcement of laws is difficult, especially in the context of scientific support for live donor as opposed to deceased donor organs.
- Deceased donor programmes require complex infrastructure, greater expense and larger human and technical resources.
- The short- and long-term risks of live donation in the best of hands are low but real. However, there are no clear data on the risks in poor facilities with poor clinical services.
- There was agreement that there should be a role for an independent donor advocate, or a variation based on resources and circumstances of the country.
- There is assumed complicity in illegal organ trafficking of a minority of trained physicians and surgeons but they have been identified in only a small number of cases as there is extreme difficulty in documenting illegal trafficking events reliably and either substantiating or refuting rumour.
- The size of the practice of organ trafficking is likely to be large and it is unacceptable for countries and professional associations to simply reject it as immoral and illegal without taking further active steps.
- The primary generator of illegal transplantation is presumed to be poverty. Organ trafficking could perhaps be given the same international legal status as child sexual abuse in both donor and recipient countries.
- Consideration should be given to limitation of organ transplantation to public hospitals.
- Insurance reimbursement for live kidney donation in a third party country should be abolished.
- WHO could consider a greater role in the care of donors, especially through the collection of data on the size of paid organ and tissue donation.

Session 6 – Tissue and cell banking

Issues in tissue banking and transplantation – Dr Yongyudh Vajaradul

Dr Vajaradul presented the status of tissue banking and transplantation in Asia with a focus on Thailand. He stated that despite considerable success in sourcing, processing and using tissue donations there are many obstacles to the effective use of tissue therapies on the continent. Several centres now exist that bank biomaterial and tissues including the recent introduction of tracheas. In the last several years there has been a progressive decrease in consent from next of kin to recover tissues. The reasons for this are unclear and need to be understood. In his opinion, major difficulties in enhancing tissue banking in Asia include a "poor cost benefit ratio in running tissue banks, a lack of formal education and training both for the user (surgeons) and producer (tissue banking technologist) and insufficient research in the region". He also expressed concern about commercialization of tissues.

There is a need for establishing international standards for tissue banking. WHO can play a role in formulating standards, promoting global or regional networks of tissue banks and assistance with promoting and improving research, education, training and clinical use of human tissues.

Haematopoietic stem cell transplantation – Dr Jeremy Chapman

Dr Chapman reported on the rapid development of haematopoietic stem cell transplantation technology and success in the past ten years. This has led to reliance on global access to volunteer donors and stored cord blood. One of the obstacles is "the tremendous diversity in human DNA" and difficulties in matching tissue. A concern is that impending regulation in many countries, based upon standard regulatory approaches, threatens to severely reduce patient access to essential treatment. The regulators' paradigm must thus include evaluation of the risk-benefit ratio for individuals and the community. It is of paramount importance that regulators create international harmonization to avoid deaths created by interventions intended to increase public safety. International communication between providers and regulators of haematopoietic stem cells is thus a priority.

Brief presentations

Haematopoietic stem cell transplantation in India – Dr Kanjaksha Ghosh

In his presentation to the delegates Dr Ghosh noted that in India barriers to haematopoietic stem cell transplantation include the level of health care infrastructure, low priority in relation to other health needs, financial hurdles and the absence of trained staff. Solutions must thus encompass training in HLA typing/immunogenetics and improving nursing care within existing centres. Also necessary are the utilization of good quality blood banks to develop unrelated donor registries with suitable ethnic representation, participation of private and charitable organizations, as well as health insurance, and research targeted at cost reduction.

Issues in tissue banking and transplantation in Japan/Quality management system – Dr Naoshi Shinozaki

Tissue banks in Japan are operated by universities or hospitals and all tissue banks are now united under the Japanese Society for Tissue Transplantation. Dr Shinozaki stated that banks function with only basic guidelines regarding fairness and family consent. There is an absence of comprehensive "legal background" with minimally manipulated tissue covered under the Law of Infectious Disease. Problems include a low donation rate and poor public awareness, lack of unified regulation and unclear distinction between regulation of tissue versus pharmaceuticals (biologics) materials. The needs in Japan include promotion of national awareness; establishment of national and international standards differentiating between human cell-based medical devices and tissue for transplantation; and a government-regulated quality system.

Special concerns in haematopoietic stem cell transplantation – Dr Carlos Soratti

Argentina has an autologous and allogeneic bone marrow transplant programme through 26 centres. Of these, seven are authorized for performing bone marrow transplants from matched unrelated living donors. Dr Soratti stated that currently 230 autologous and 130 allogeneic BMTs are carried out each year. The high cost of the BMT abroad, consequent family disruption and the diverse native ethnic origin have supported the need for efforts to increase self reliance and the creation of a local donor registry. He

recommended that WHO could promote the development of regional bone marrow donor registries.

Issues in tissue banking and transplantation – Dr Eda Bloom

Dr Bloom provided the USA perspective on tissue banking and transplantation. She said that the widespread and complex use of human tissues and cells has led to concerns with respect to the direct transmission of communicable disease, control of processing, ensuring clinical safety and effectiveness, overseeing promotion and labelling and monitoring through inspection. Policies to address many of these concerns are still evolving within the US Food and Drug Administration. In the USA there is some "resistance to greater government oversight." In her opinion, four criteria determine the level of regulation: more than minimal manipulation, non-homologous use, combination products and systemic effect, but difficulties with a clear definition and use of these terms has led to the need to provide both flexibility and consistency of oversight. WHO can help at an international level by facilitating consistent policies that do not compromise safety and effectiveness but facilitate the import and export of tissues and cells.

General discussion – Consensus points

- International data exchange on therapeutic use of human tissues is poor with little data on utilization, as well as lack of harmonization and high costs for tissue banks to achieve regulatory standards.
- Poor levels of education, training and research in tissue banking, inconsistent approaches to donor consent, limited or non-existent evidence of efficacy in some tissue transplantation and tissue commercialization are further concerns.
- There is a need to address concerns about the self-sustainability of "not-for-profit banks" on the one hand and excessive income of "for-profit banks" in the context of altruistically-donated human material.
- Harmonization of international regulations of haematopoietic stem cells is critical and should be achieved through global communication between regulators and providers, development of global professional standards, the registration of serious donor adverse events and the continuous measurement and publication of transplant outcomes.
- WHO has potential roles to facilitate communication between the regulators and providers of haematopoietic stem cells and to facilitate an international workshop on tissue banking.

Session 7 – Quality and safety in the transplantation process

Basic requirements for organ transplantation – Dr Ryota Shirakura

Dr Shirakura reported that Japan has performed 15 113 renal transplants since 1964, 2411 liver transplants since 1989, but only 17 heart and 39 lung transplants since 1998. The organs have largely been obtained from living and to some extent from non-heart beating donors. There still remains an extreme donor shortage from brain dead donors. It is believed that the strict Japanese Transplantation Law, although addressing brain death

criteria, may have reduced these donation rates. Consent largely for non-heart beating donation leads to high rates of primary non-function and death is frequent on the heart and lung transplant waiting lists. Patients with failure of the liver or kidney have to rely on non-heart beating or living donors. He stated that the shortage of deceased donors has resulted in long waiting lists (currently 12 862 for kidneys) and many Japanese travel abroad for transplantation through arrangements with foreign transplantation services where they are included in waiting lists. This is the case in particular for children under 10 years of age as the transplantation law in Japan does not allow organ donation by persons younger than 15 years old.

Core technical principles in transplantation – Dr Laura St Martin

Dr St Martin emphasized that human organ transplantation is an expensive form of therapy where successful outcomes require high levels of expertise, careful monitoring of recipient and recipient compliance. The best use of donated organs requires careful candidate selection and timing and active management of patients waiting to be transplanted. Rapid tests are needed for organ donor evaluation and screening. Consideration should be given to the matching of "extended criteria" donors with appropriate recipients and quantifying the risk related to receiving these organs. Government oversight and regulation should require minimum qualifications for transplant surgeons and physicians, minimum ancillary and support services, together with minimum standards for organ donor evaluation, screening and documentation.

Canadian national standards for all transplantation – Dr Paul Dubord

Dr Dubord reported that Canada is working on an approach that reduces the problems with multiple standards by unifying standards, directives and regulations for all organs, tissues and cells. Canada has developed one National General Requirements Standard covering all areas of donation and transplantation (Z900.1), with five subset Standards: Tissues for assisted reproduction (Z900.2.1); Tissues for transplantation (Z900.2.2), Perfusable organs for transplantation (Z900.2.3), Ocular tissues for transplantation (Z900.2.4) and Lymphohaematopoietic cells for transplantation (Z900.2.5). The process used to achieve this goal has been to involve and obtain a consensus among professionals, government and the general public through various modalities including the internet. The General Standard and associated subset Standards for all Cell, Tissue, Organ Transplantation and Assisted Reproduction, were declared National Standards by the Standards Council of Canada. Health Canada is currently preparing a regulatory framework referring to the standards in regulation for Federal Health Care responsibilities. This will then govern Health Canada's inspectorate responsibilities.

A project is under way to develop a National Surveillance System for all Cell, Tissue and Organ Transplantation and Assisted Reproduction for all transplant activity in Canada. As well, a programme is under way to evaluate various compliance models to ensure that facilities and end-users are complying with the transplantation safety standards.

Brief presentations

Brazil – Dr José Antônio de Faria Vilaça

Dr Vilaça reported that the constitution of Brazil includes the law (Article 199) that provides for the conditions and requirements which facilitate the removal of organs, tissues and human substances for the purpose of transplants, research and treatment, as well as the collection, processing and transfusion of blood and its by-products. All types of sale are forbidden by law. Dr de Faria Vilaça noted that in order to increase the effectiveness of transplantation there is a need to update regulation concerning organ and tissue quality and establish standards for surveillance. Also needed are closely observed clinical and laboratory criteria for donors and provision of adequate information to society and users.

Good practices for tissue banking – Dr Eda Bloom

Dr Bloom noted that in the USA tissues are not regulated in similar ways to drugs. There is a clear need to regulate good practices with respect to tissue banking as evidenced by instances of many recent transmissions of infectious diseases. Problems include an absence of adverse event reporting, large numbers of small banks and inadequate "tracking" processes making it difficult to trace tissues from donor to recipient (due to privacy issues). Industries have standards in place but "these are voluntary and thus not enforceable". Adverse effects are often not reported to the US FDA. Other obstacles include the expense and difficulty in validating current processes. Regulations need to be the least burdensome to implement while enhancing safety. She stated that the US FDA is developing a model of Good Tissue Practices which they will be willing to share with other WHO member countries.

Egypt – Dr Ibrahim Badran

Dr Badran gave an account of shared difficulties "within the realities of developing countries", including Egypt. A degree of economic and political "stability" and commitment to human rights are essential for the success of transplantation programmes. Other difficulties include "difficulties in convincing all Moslem religious leaders to accept brain death criteria". Poverty, unless ameliorated, will continue to engender the buying and selling of organs. While there are trained Egyptian medical staff, many settle overseas. There is a need for an appropriate legal framework, especially with respect to concerns over the diagnosis of brain death. Dr Badran stated that to set up basic cadaveric donation programmes would require a widespread upgrading of clinical facilities and human resources throughout the health system, much of which is currently unachievable economically. WHO can assist implementation of affordable transplantation through the development of novel approaches to reducing costs such as generic drugs for immunosuppression.

Council of Europe (CoE) – Mr Karl-Friederich Bopp

Mr Bopp explained that the Council of Europe, which is not a European Union body, has issued a number of recommendations on organ and tissue transplantation. These have come through the convention for the protection of human rights and dignity for the human being with regard to the application of biology and medicine (Bioethics Convention), Oviedo, 4 April 1997, the protocol on transplantation of organs and tissues of human origin, Strasbourg, 24 January 2002, and Recommendation (2001) 5 on the management

of organ transplant waiting lists and waiting times. Recommendation (2003) 10 on Xenotransplantation and Recommendation (2003) 12 on organ donor registers, were produced earlier this year. Most of the recommendations, however, are not legally binding on European countries. The CoE has also published the 1st Edition of Guidelines on Safety and Quality assurance in organs, tissue and cells, replicating the work in blood transfusion medicine. The CoE supports annual transplant and donation data collection and publication and a European Day on Organ Donation and Transplantation to raise public awareness.

General discussion – Consensus points

- There was concern about the creation of two levels of donors and potential recipients through the description of donors and recipients as extended or marginal. However, it was accepted that in some instances it may be appropriate to transplant organs from virus-infected donors into virus-infected recipients.
- Concerns were expressed by some about definitions and safety issues when considering matching "extended criteria" donors with appropriate "extended criteria" recipients. There was a need for early identification of those who would agree to accept extended criteria donor organs for whom "any kidney is better than no kidney". Recipients should be informed of the risks and benefits of accepting such an organ.
- In countries with high levels of HIV infection of patients the question arises as to how to allocate kidneys to patients with lower chances of success such as those infected with HIV.
- It was highlighted that there is geographic variation in risk of endemic diseases that may be transmitted through transplantation.
- Roles for WHO could include: creation of a global map of the safety measures that should be performed on donors and donation from different regions of the world; encouraging the harmonization of core standards in quality management in donation and transplantation processes; and helping to develop Member States' capacity for national regulatory approaches to quality and safety

Session 8 – Xenotransplantation

Safety and availability of xenotransplantation – Dr Abdallah Daar

Dr Daar noted that the primary challenges of xenotransplantation remain scientific at the present time, but added that the challenges also include ethical, legal and social issues. There are many significant concerns that require public debate prior to the first scientifically successful application that have been identified. These include animal welfare, equity of access to therapy, management of the small risk of xenozoonoses with large potential public health consequences, as well as short and long term surveillance needs. The form of consent needed for the patient and his contacts must take into account not only individual issues but also public issues, thus taking on the nature of a "Ulysses" contract, the contract that Ulysses made with his crewmen to restrain him, regardless of how much he objected, when he faced the Sirens. Dr Daar believed that the Canadian

experience of public engagement has been instructive and has halted clinical xenotransplantation in that country at the current time. What is needed is “public engagement rather than public education” when considering policies. There is a need for agreement on risk evaluation methodologies and the application of global governance with harmonization of databases and archives to minimize global risks and maximize knowledge and research.

National and international policies – Dr Eda Bloom

Dr Bloom began by defining and providing illustrative examples of xenotransplantation, according to the USA definition of xenotransplantation as "any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissue or organs from a non-human anima source or (b) human body fluids, cells, tissues or organs that have had ex-vivo contact with live non-human animal cells, tissues or organs". This definition was developed to encompass the broader range transplantation circumstances that pose a risk of transmitting xenogeneic infectious agents to humans. She also stated that “xenotransplantation has specific issues” that set it apart from organ and tissue allotransplantation. These issues include the possibility of transmission of known and as yet unrecognized xenogeneic infections from animals to humans. For example, based on the findings that porcine endogenous retroviruses (PERVs) could infect human cells in vitro, in 1997 the USA halted all clinical trials in porcine xenotransplantation until those conducting the trials provided data to demonstrate their ability to perform appropriate tests and updated their Informed Consent documents to reflect the PERV risks. Dr Bloom gave an account of the collaboration on xenotransplantation within the USA among the components of the Department of Health and Human Services. The US Food and Drug Administration has produced three guidance documents on xenotransplantation and there is a Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation. Dr Bloom summarized the OECD consultation on xenotransplant surveillance systems in 2000, which reached consensus on a number of areas, especially on the development of an international surveillance network. She stated that potential roles for WHO might include the development of consensus on basic principles of safety and oversight with the encouragement of nations to support those principles, development of agreement to monitor and control the travel of recipients for xenotransplantation and implementation of a xenotransplantation surveillance system. WHO may also help to identify countries in which xenotransplantation occurs and encourage regulation with an accepted minimal framework for oversight. There is also a need for the development of general recommendations for obtaining informed consent in situations that may represent a risk to the general public and the holding of international consultations to consider when public health risks may override individual rights.

Brief presentations

Xenotransplantation in Mexico – Dr Arturo Dib-Kuri

Dr Dib-Kuri gave a brief report of xenotransplantation activities in Mexico. Research in this area has occurred within Mexican universities in collaboration with institutions in other countries such as New Zealand. Clinical work has included the transplantation of pig islet cells with barriers into humans with Diabetes Type 1. After two years there have been

no instances of infection and patients have shown "some decrease in insulin requirements". Mexico has a strict law for the safety and protection of human subjects, with the requirement for mandatory submission of progress reports every month.

Council of Europe approaches to xenotransplantation – Mr Karl-Friedrich Bopp

Mr Bopp reported that short recommendations were introduced in 1997 to draw Members' attention to xenotransplantation procedures, followed in 1999 by Recommendation 1399 of the parliamentary assembly calling for a moratorium. An expert working party was subsequently established (under two standing committees, CDBI/CDSP) to produce Recommendation (2003) 10 on xenotransplantation which is to date a "state of the art" document. This will include definitions similar to those used in the USA and include requirements and conditions for regulation and implementation of xenotransplantation, including close and continuous surveillance of recipients.

Japanese approaches to xenotransplantation – Dr Tadahito Kanda

Dr Kanda reported that the first Japanese Public Health Guidelines on the issue of potential infections related to xenotransplantation were published on 9 July 2002. The guidelines made note of the prior treatment of patients with cells exposed to mouse keratinocytes and supported the accumulation of data from all human clinical trials as the most effective basis for understanding the risks. Dr Kanda recommended "flexibility" in formulating global guidelines depending on the nature and type of xenotransplantation. He also emphasized the need for an international database on infections following xenotransplantation.

Canadian approaches to xenotransplantation – Dr Maura Ricketts

Dr Ricketts provided a brief account of the approach that Canada has taken towards xenotransplantation. At present xenotransplantation is a regulated procedure in the country. The first draft for Proposed Canadian Standards was completed in 1999, followed by workshops on xeno-surveillance in 2000. Public involvement was sought through a Public Advisory Group. As a result of these processes, cessation of all clinical trials and a moratorium on xenotransplantation was called for in 2000. In 2002, the Issue Analysis was completed, recommending the implementation of precautionary measures prior to any clinical trials; final Canadian regulations are awaited. According to Dr Ricketts, the "Canadian approach" recognizes the urgency of establishing effective regulation and surveillance plans prior to the first effective clinical application, especially because of the potential for rapid and widespread dissemination of such an application.

General discussion – Consensus points

There was consensus that there was a need to act internationally prior to clinical evidence demonstrating success of xenotransplantation to ensure that "guidelines are in place as soon as possible" in all states in which xenotransplantation occurs. In view of the continuing shortage of allografts, xenograft organ and tissue transplants have the potential for tremendous good by providing "an unlimited supply" of organs and, if the approach is proven successfully, may be rapidly and widely used. It has the potential for "changing the world". A cautionary note was expressed by some that xenotransplantation is an expensive high technology endeavour that will be accessible to only some rather than to many and

that it thus has the potential to "widen the gap" between the affluent and the poor nations. It also has the potential to introduce novel infectious diseases into the human population.

There was a consensus that WHO can play a significant role and could consider the following:

- Encourage nations to support consensus on basic principles for xenotransplantation safety and oversight.
- Identify countries in which xenotransplantation occurs and support the approach that regulation must be in place in all countries in which clinical trials of xenotransplantation occur.
- Develop general recommendations for obtaining informed consent in situations that may represent a risk to the general public and in which individual rights and public good may come into conflict.
- Develop and encourage nations to support agreement to monitor and control travel of recipients for xenotransplantation.
- Implement an International Xenotransplantation Surveillance network along the previously discussed lines.

Session 9 – Efficacy, access and allocation

Pakistan and live renal transplantation: Moral dimensions of access and allocation – Dr Farhat Moazam

Dr Moazam provided a background to the nature of health service delivery and insufficient government dialysis and transplant programmes. The void is being filled by a rapidly expanding private sector, many using unrelated paid donors. In the absence of health insurance, the costs of dialysis – US$ 40- 50 per session, transplant US$ 8000-10 000 and medications at US$ 300 per month – remain beyond the means of the majority. She contrasted this with the success of the Sind Institute of Urology and Transplantation (SIUT), a "unique" model of "government-community partnership" (40% financial support from the government, the rest from donations and endowments), that utilizes indigenous moral norms of culture and religion to promote renal transplantation. Pakistan presents a deeply religious, family centred, hierarchical, collectivistic culture with several generations pooling resources for survival. SIUT relies on cultural and religious emphasis on obligations and duties to the extended family rather than autonomy and rights of individual members. It accepts only genetically related donors with the belief that healthy family members have a duty to come to the aid of kin in danger of losing their lives. Reluctant donors are approached with reasoning, reassurances, coaxing, scolding and "shaming" for dereliction of familial and religious obligations. SIUT is now the busiest centre in the country, carrying out over 100 renal transplants every year.

Impact of international collaboration – Dr Esmeralda Luciolli/Dr Driss Zaïd

The presenters stated that in Morocco only 20% of all patients can be treated and that transplantation is only carried out in public institutions. They described the success of the collaboration between French and Moroccan services that was established to support development of transplantation. Each year 15-20 Moroccan professionals are sponsored

for fellowships in France in areas including nephrology, urology and anaesthesia. The programme involves a comprehensive approach to medical and surgical staff training, the local clinical environment and laboratory capacity. 'Key points' in the success have been the role of the Ministry of Health and hospital administrations in helping the establishment of a legal framework for organ donation to support the development of kidney transplantation from living donors in the first phase and subsequently from cadaver donors, using a practical approach and above all 'mutual trust' among those involved in the programme. Issues that still remain are how to provide equitable access to transplantation and drugs for the population and to initiate a cadaveric organ programme. A similar collaboration between France and Tunisia led to the creation of a National Transplantation Agency, coordinating procurement organization in hospitals, the development of tissue banking and liver transplantation.

Cornea banking in East Africa – Dr Ashok Shah

Dr Shah gave an overview of the status of corneal banking in East Africa as well as in some of the western African countries. Corneal scarring remains a high cause of blindness but there are currently only three eye banks in Kenya and some in South Africa. Corneas are still largely obtained from Sri Lanka and from the USA. The number of keratoplasties remains insufficient with the result that waiting lists continue to rise. The major difficulties are lack of trained ophthalmologists (around one per million population) and nurses and cultural and religious barriers to local donation of corneas. Solutions include increasing donor tissue availability, providing more trained personnel and developing tissue banking and ophthalmologic infrastructure. Dr Shah believes that WHO's role could include advocacy, sensitizing governments, helping in collecting database material and "capacity building".

Brief presentations

Evidence-based transplantation policy development: USA – Dr Laura St Martin

Dr St Martin emphasized that given the known shortage of organs it is vital to "ensure their best use". The need to prioritize patients requires comprehensive databases with donor and recipient information and outcomes, equity of access to transplantation including access for "special populations", continuous evaluation of policies with changes based on evidence of effectiveness. Important elements include the sharing of data and research using comprehensively collected and analysed minimum datasets. The obstacles to achieving this include the financial and human resources necessary to develop and maintain databases and the expertise needed to perform sophisticated statistical analyses.

South Africa – Miss Nettie Mbatha

Miss Mbatha informed the participants that health management and financing have been major challenges for South Africa since 1994. The post-apartheid era has seen many problems in providing health care, particularly for rural blacks. Although the country is classified as "middle income" by the World Bank, the socioeconomic context in reality encompasses a minority of rich and majority of poor people. Despite limited resources the Government supports transplantation as "essential intervention" for end stage organ failure, but many on dialysis in the public sector cannot be transplanted. On the other hand, the

private sector provides faster service in transplantation without other selection criteria. This therefore raises issues both of "ethics and constitutional rights". Resource constraints combine with the HIV pandemic to reduce organ donations which is further strained by the influx of patients from neighbouring countries who often bring their own donors. Other problems are related to poverty, illiteracy, local belief in indigenous medicine and concerns about organ trafficking and health tourism. A National Health Bill is being drawn up to address many of these problems and to work towards an integrated policy on organ transplantation in the country.

Perspectives in transplantation: Senegal – Dr Boucar Diouf

Dr Diouf informed the participants that it is estimated that the Senegalese population of 10 million has approximately 800 identified new cases per year of end stage renal failure. A total of seven patients have been transplanted, all overseas, and two live in Senegal. Barriers to transplantation include insufficient medical staff, absence of HLA typing and cross-matching, no renal angiography and absence of financial resources. Extensive sub-Saharan and intercontinental collaboration will be required to change the outlook. The Government is hoping to begin dialysis procedures in December 2003.

Transplantation: Russian Federation – Dr Nikolai Tarabarko

Dr Tarabarko reported that currently there are five transplant centres in the Russian Federation. The largest in Moscow undertakes approximately 500 kidney, 100 heart and 15 liver transplants from living donors. Donor sources vary between the centres with St Petersburg using approximately 50% deceased (brain dead) donors. Moscow, on the other hand, obtains 90% from non-heart beating donors. The human organ and tissue legislation (1992) requires that living donors must be over 18 and genetically related. Thus paid donation using Russian donors can only occur outside the borders of the country.

General discussion – Consensus points

- Prevention of renal disease is by far the most cost-effective approach to population health.
- High prevalence of renal disease implies that it will be present both in recipients and in potential donors.
- Funding of transplantation programmes must be sustainable and inclusive of long-term drug costs.
- There is a need to identify and disseminate the information on successful "models" of transplantation that use local resources and cultural norms. Success will not come from the provision of isolated components of support but should involve the comprehensive support of individuals and programmes extending throughout legal, social and clinical aspects of transplant programmes.
- Need for "alliances" between institutions with the approval and help of transplantation societies and WHO. North-to-south but also "south-to-south collaborations" are needed.
- WHO's role could include facilitating alliances between national transplantation organizations in Member States involving cooperation at legal, ethical and technical levels.

- WHO may assist the development of agreement on minimum datasets needed to support evidence-based transplants and allocation policies.
- There is a tremendous need for considering ways in which to increase corneal transplantation in the developing world. The resolution of quality issues in corneal transplantation is needed since anecdotal reports include failure rates of up to 50%. WHO possible roles in corneal donation include advocacy, support to identifying relevant needs and to capacity building.

Session 10 – Regulation and government oversight of transplantation

Difficulty in defining and achieving safety in the EU – Dr Bernard Loty

Dr Loty gave an overview of steps taken within Europe to achieve regulation and safety in transplantation. Recent European approaches have been discussed at the Conference on Safety and Quality in Organ Donation and Transplantation in the European Union (Venice, September 2003). It is recognized for most people that an organ transplant extends life expectancy and can dramatically improve the recipient's quality of life. Because of the organ shortage, all available organs should be considered for transplantation as a recipient whose life is in danger may be willing to accept a risk of disease transmission or organ failure. Therefore a specific approach to safety and quality is required. Since no organ is perfect and all will carry some risk of failure or transmission of disease, any approach to regulation implies the balance of risks and benefits, including the risk associated with the organ versus the consequences of not getting a transplant. Concerning regulations on tissue and cell transplantation in the EU, Dr Loty reported that the "borders" between these and medical devices and medicinal products are still not clearly defined. The European approach to somatic cell therapy medicinal products is defined by Directive 2003/63/EC – medicinal products for human use, including five categories of human cells used therapeutically. In Dr Loty's opinion, countries that already have regulations in place need to "harmonize" the regulations that are sometimes "excessive". Many developing countries on the other hand, often lack clear regulations. This needs addressing so that transplantation does not occur in the absence of regulations.

Issues in regulations: experience of the Republic of Korea – Dr Kyu-Won Jung

Dr Jung reported that the Transplant Act was first passed in 1999 and then reviewed in 2002. The Act covers organs and tissues (only bone marrow (BM) and corneas). Family decisions are given importance in cadaver donations and organ donation rates appear to have dropped after the Transplant Act. Living donors are under pressure from the family particularly to donate to sons. The autonomy of donors under 20 years is not protected well enough. There is also a practice of buying and selling and "swapping" organs. A new bill addressing tissue transplantation beyond cornea and BM and prohibiting the sale of organs and tissues has been discussed, but it has yet to be passed by Congress. Private cord blood banks have been established without control or informed consent. Xenotransplantation research has been funded by the Government but is not yet regulated. A bill addressing bioethics and biosafety and prohibiting heterogeneous nuclear transfer is also awaiting passage by the Government.

Brief presentations

Argentina – Dr Carlos Soratti

Dr Soratti stated that Argentina has had a Procurement and Transplant regulation law since 1977 with strict State regulation and fiscal control of procurement, allocation and destination of organs and tissues from living or deceased donors. Family refusal of deceased donation is over 60% and a high percentage of citizens express their opposition to signing on as organ donors when requested at the Official Registration Office. The challenge for Argentina is how to promote altruism, engender public trust and maintain transparency within programmes. Dr Soratti believes that from an Argentinian perspective it is important that WHO promote strong opposition towards incentives for donation and use of non-related living donors, while encouraging and promoting international surveillance of altruistic organ donation.

Mexico – Dr Arturo Dib-Kuri

Dr Dib-Kuri informed the delegates that over 30 000 tissue and organ transplants have been performed in the 242 authorized national centres in Mexico since 1963. The current rate of transplants is 4000 per year but there are still 5000 patients on the cadaver waiting list and demand still exceeds donation. The National Transplantation Center created in 2000 and the National Registry and Laws control all transplantation in the country so that Mexico has an "absolute, supervised system". Dr Dib-Kuri stated that currently 85% of transplants are Government-funded, but there are insufficient resources and hospital facilities to meet patient needs. An increase in deceased donation rates is a Presidential priority. WHO can help by advising governments to increase transplant budgets, hold a "World Day on Transplantation" and advise on the development of policies regarding donation and therapeutic use and research on cells, tissues and organs and on cloning.

Colombia – Dr Klaus Mieth

Dr Mieth stated that Colombia has a National Health System with a donor rate of 5.3 pmp. About 44% of cadaveric organs are obtained through "presumed consent" after a wait of six hours for families. Human tissue banks in Colombia must be associated with a hospital or health care agency. Tissues cannot be subject to commercial transactions and the export of tissue is forbidden. Interchange with regional banks or transplant programmes can be carried out for humanitarian reason with special permission. Dr Mieth felt that there is a need for international networks, international (regional) collaboration, education and promotion of transplantation, as well as for agreement on essential safety and quality principles and harmonization of legislation and regulation.

European Union policy – Dr Eduardo Fernandez-Zincke

Dr Fernandez-Zincke presented an overview of the draft of the Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells. This encompasses quality and safety, ethical aspects, inspection and accreditation, traceability and import and export. In addition, the comprehensive Directive addresses quality and safety standards, selection criteria for the donor and the recipient, laboratory tests required for donors, cell and tissue procurement procedures and reception at the

tissue bank, tissue and cell processing, as well as preservation and distribution. It includes ethical principles that must guide voluntary and unpaid donation, procurement on a non-profit basis, mandatory consent and information, data protection and confidentiality. It will be required that countries provide competent authorities and accreditation and inspection structures, supervision of tissue procurement, accreditation and registration of tissue banks and inspection and control measures of both import and export.

General discussion – Consensus points

- There is considerable global disparity and diversity in the level and extent of government regulation and oversight of both donation and transplantation of organs and tissues.
- A national transplantation agency constitutes a possible model for effective integrated development of donation and transplantation.
- There is an agreed need to have global safety and quality principles for the regulation of organs and tissues.
- There is a relationship between the mechanisms of funding clinical activity and the level of regulation and oversight.
- Regulation of health tourism is a relevant strategy to inhibit illegal organ trafficking.

Breakout groups and consensus points

Procurement of organs and tissues from deceased donors

Breakout group report

The issues can be considered within a limited number of fields:

Legal framework including criteria to certify death; the means for consent/objection to donation; ways to designate/authorize/certify transplant centres and personnel to remove organs and tissues; ways to record and maintain traceability; definition of reasonable costs and charges associated with recovery and processing of organs and tissues; and basic principles for allocation. WHO could recommend to the Member States the points to be covered by national regulations as minimum requirements.

Technical aspects including development of core standards to ensure quality of tissues and organs as well as expertise of the procurement teams; promotion and support of appropriate training and technology as well as accountability of performance; and advocate regional collaboration.

Organizational aspects including promotion and support of the establishment of local/regional tissue banks, management training for self-sufficiency, promotion and support of research and technology, traceability systems and professional and general public awareness.

WHO could assist in the development of the necessary materials, identify best practices and disseminate information.

Political advocacy. Member States should be sensitized to the need to strongly support organ and tissue procurement from deceased patients; advocates for transplantation should impress upon governments the value of utilizing this resource.

General discussion – Summary of consensus points

- Transplantation is effective and should be seen as a "global patient service".
- Data on deceased donor transplantation from some regions and countries are missing, inadequate, or non-inclusive.
- "Disquieting discrepancies" exist between countries and regions with respect both to the number of transplants performed PMP and the source of donors. The reasons are unclear but are likely to be complex.
- Widespread reluctance to donate cadaveric organs was noted in many countries throughout Africa, Asia and Latin America, even when appropriate legislation exists. Factors include both the technical (financial constraints, paucity of skilled staff, inadequate infrastructure) as well as important indigenous cultural and religious beliefs and values.
- Some countries still lack legislation recognizing determinations of death based on neurologic criteria and legislation governing transplantation.
- Societal trust remains a crucial aspect for a successful donation and transplant programme; therefore programmes must focus transparently on ethics, access and safety.
- The use of executed prisoners as "planned cadaver donors" continues in more than one country. It is viewed as a coercive and thus unacceptable situation in which to obtain consent.
- There are important geographic variations in risk of infectious and other diseases that may be transmitted through transplantation.
- Concerns were expressed by some participants about definitions and safety issues when considering matching "extended criteria" donors with appropriate "extended criteria" recipients. There was a need for early recognition of patients who would agree to accept extended criteria donors for whom "any kidney is better than no kidney".
- In countries with high levels of HIV infection of patients the question arises as to how to allocate kidneys to patients with lower chances of success such as those infected with HIV.

- Potential roles for the WHO include:
    - Addressing the fact that live donations are increasing globally despite the preference expressed in 1991 Guiding Principles for cadaveric donation.
    - Facilitating better national, regional and global data collection and analysis.
    - Fostering qualitative, empiric research in diverse cultures to better understand the global discrepancies in the source of organs for transplantation.
    - Encouraging and facilitating governments to have appropriate legislation and oversight mechanisms in place.
    - Helping to develop Member States' capacity for national regulatory approaches to quality and safety.

- Creating a global map of the safety measures that should be in place to ensure the quality and safety of donated organs and tissues from different regions of the world.
- Encouraging the harmonization of core standards in quality management in donation and transplantation processes.

Living organ donor programmes

Breakout group report

The group emphasized the need to aim for realistic goals, map current issues, identify areas of consensus and develop recommendations for WHO's role. Current status: there was broad agreement that live donors now provide a significant number of organs worldwide (particularly in developing nations) but there are unclear, insufficient data (except from some developed regions) as to the extent of this practice. It is necessary to obtain and compile data, in particular from developing countries. A worldwide registry of living donors is unrealistic but WHO could recommend and facilitate local and national registries, possibly with the help of existing international professional bodies. There was consensus on this.

The "invisible" living donor: to date the focus has been largely on the recipient. There was wide consensus that the "invisible" donor also needs to be brought onto centre stage. Data on safety of donor nephrectomy obtained from developed countries (i.e., low morbidity and mortality) is quoted to potential donors in countries where the underlying health status of the population and health systems may not be optimum. There was consensus that "real" and global data are needed – WHO could encourage governments and health organizations to assume responsibility for this. Long-term surveillance after donation is needed for morbidity/mortality results and qualitative, empiric research for emotional and psychological outcomes as well as public attitudes and beliefs. Minimum standards for potential donors must be established. Physicians should assume greater responsibility for donors, along the lines of their organ-recipient patients. An independent "outside" advocate for donors was considered to be of importance, but indigenous constraints (staff, culture, education) may require diverse forms of advocates in countries.

Genetically related donors: participants from family-centred countries of Latin America and Asia noted the many advantages of live, genetically related donors. Such donations can provide better matching, decreased need for immunosuppression (less costs), as well as obligations of family to the related donor who may be less likely to get "lost". There was consensus that this form of donation will continue and should be encouraged.

Incentives/disincentives: the important question was raised regarding how and where (and whether it was possible) to draw a line between removing disincentives and providing incentives. When does the (ethical) first become the (questionably ethical) second? Local realities can have a major impact on this, e.g. if a donor in a country with no health insurance gets a complication, who pays? And would this qualify as an incentive or removing a disincentive? No consensus could be reached on this issue.

Buying/selling organs: there is a kind of continuum (suggested by Dr Groth during subsequent discussions) that runs from voluntary, altruistic donation (good, laudatory, to be encouraged), to buying and selling (bad, ethically questionable, how should it be addressed), to organ trafficking (evil, must be stopped). Buying and selling is occurring in many countries but "there are no data on the size of this puzzle". Some in the group noted that condemning this practice morally has been a fruitless effort and has driven the practice underground. It was time to address this, according to this minority opinion**,** not via prohibition and censure but through regulation by individual countries based on their own situations. In contrast, a number of participants (particularly from developing countries) continue to see this as unethical. Reasons given included that countries are not "enclosed islands" and that sanctioning in any form by one would lead to commercialization across borders with generally poorer countries as losers and diminish altruistic donation. It was also suggested that a move in this direction would contravene legislation against buying and selling introduced in many countries under the influence of the 1991 WHO GP. Despite lack of unanimity, the consensus favoured continuing prohibition.

Trafficking of organs: there was consensus that this must be seen as a criminal activity that has not only adverse repercussions for individuals but also social, economic and political ramifications. It should be criminalized along the same lines as trafficking in humans; international agreements may be needed to address countries that supply organs, those that receive and the "brokers" involved in the transactions.

General discussion – Summary of consensus points

Donor safety

- Minimum standards (physical, emotional and psychological) for the evaluation and selection of potential donors and recipients must be established.
- The presence of a high prevalence of renal disease in a country or region implies also a high likelihood of renal disease in potential donors.
- The safety of donating a kidney or lobe of liver remains uncertain both in the short and long term. Data suggesting low morbidity and mortality following donor nephrectomy have been obtained from the developed world although adverse outcomes are probably under-reported, even in the USA. These data are used by physicians and institutions in the developing nations to convince donors of the safety of the procedure, even though the situation (poverty, malnutrition, high infection rates, poor and inaccessible health care) is vastly different across countries.
- There is almost no information on short-term morbidity and mortality of donors from many countries; such data must be collected at a national and regional level and is the responsibility of local health care organizations, medical associations, governments.
- The donor becomes effectively invisible very soon after donation. Monitoring of long-term outcomes has been largely focused on the recipient. It was agreed that donors should also be offered long term surveillance post-nephrectomy as patients requiring closer involvement by physicians.
- Long-term qualitative and anthropological studies of donors are needed.
- Participants agreed that, with a number of specific exceptions, there is no clear record as to the number of live organ, cell or tissue donors each year and that there is a need

to begin attempts to obtain these data, though the concept of a global registry of live donors is probably impractical.

- It was agreed that WHO could recommend and facilitate donor safety data collection at national and regional levels.

Motivation of donors

- It was agreed that there is a continuum of motivation from altruistic, voluntary, and unpaid cell, tissue and organ donation—which is good, laudatory and to be encouraged—to financially motivated trafficking in organs, cells and tissues—which is evil and must be stopped.
- The advantages of confining donation to genetically related donors are significant, particularly in developing countries; these include better reassurance of altruistic motivation to donate, better HLA matching, better long term graft survivals, potential reduction in immunosuppression, and a better chance that the donor will not be lost in follow-up.
- Altruistic living donation of kidneys from people other than those who are genetically related to the recipient is a widely accepted practice in Member States. Living donors of organs other than the kidney (partial lung, liver and pancreas) largely remains confined to genetically related donor/recipient pairs.
- The genetic relationship between the donor and the recipient does not guarantee an altruistic relationship; coercion and financial reward occur, irrespective of safeguards.
- A recommendation that there should always be an independent advocate for donors was felt to be impractical, especially in poorer countries; but the concept should be considered as important by Member States, for adaptation to local circumstances and cultures. For example, in some clinical environments consent from living donors is undertaken by third party physicians and surgeons not involved in the care of the recipient before or after transplantation.

Buying/selling and trafficking

- The scale of illegal transplantation practice is likely to be large and it is now unacceptable for both Member States and professional associations to simply reject it as immoral and illegal without taking further active steps to prevent it.
- The primary motivation for, and instigation of, illegal donation is presumed to be poverty.
- There is assumed complicity of a small minority of trained physicians and surgeons, but they have been identified in only a small number of cases There is extreme difficulty in documenting illegal trafficking events reliably and either substantiating or refuting the rumour.
- It was agreed that organ trafficking should be seen as an increasingly common criminal activity with individual, social, economic and political repercussions, akin to transnational trafficking in humans for other purposes (such as children for sexual abuse or adoption, males for forced labour, and women for prostitution). The laws in Member States should therefore address issues of the supply, receipt, and brokerage of trafficked organs and tissues.
- The conceptual difference between removing disincentives and giving incentives was highlighted. It is not clear when the first process, which was deemed to be acceptable,

becomes the second. Local realities may influence these issues in different ways. It was not clear, for example, whether offering free health insurance (to cover post-operative complications) is an unacceptable incentive for donors in a country that has poor public provision of health care. No consensus was reached on these issues.

- Potential solutions that were considered included:
  - Giving organ trafficking the same international legal status as child sexual abuse in both donor and recipient countries.
  - Limiting organ transplantation to publicly-funded and managed hospitals.
  - Abolition of insurance reimbursement for live kidney donation that is undertaken in another country (where organ trafficking is known to occur).
- Some participants suggested that the commercial traffic in organs, cells and tissues should be regulated by individual countries based on their own situations, rather than prohibited globally. However, the majority of participants, especially those from developing countries, strongly supported the view that the entire practice of commercialization of organs must continue to be declared illegal and unethical if there is to be a global reduction in the human toll from donation.

Xenotransplantation

Breakout group report

It was agreed that no nation should undertake any xenotransplantation in humans without an appropriate regulatory framework and surveillance. It was agreed that prompt action is needed in advance of the first successful xenotransplantation because of the high speed with which such a therapy may be disseminated.
WHO could therefore:

- Develop and encourage nations to support consensus on basic principles of safety and oversight.
- Provide existing national documents as models for countries that do not have current documents.
- Devise a means to involve national authorities in the regulation of xeno-transplantation, with as clear as possible a message to Member States.
- Provide a means for interaction and communication among nations.
- Produce a WHA resolution that countries would not perform xenotransplantation unless they have a framework for regulatory activities, including animal husbandry, patient and animal testing and follow-up activities, including a recommendation to prohibit "xenotourism" (travel abroad to obtain a xenotransplant).
- Review and revise as necessary and/or redistribute 1998 WHO recommendations.
- Identify funding and external partner(s) to assist in this, such as professional/scientific associations (Transplantation Society, International Xenotransplantation Association) and other international organizations (EU, CoE, OECD).
- Recommend that each country develop their own protective measures, as part of their own national recommendations. Any physician seeing a patient who has undergone a xenotransplantation procedure in another country should have the responsibility to report that procedure to their own national public health authorities, respecting the

privacy and confidentiality regulations of their own country. The physician and the patient should then follow the relevant national regulations and guidelines of the country in which they are resident.

- Any physician performing a xenotransplantation procedure on a patient returning to another country should report that procedure to their own national authority, which should report to the home country of the recipient.
- A xenotransplantation surveillance system should be developed.
- Countries should develop national surveillance systems to keep track of individual xenotransplantation events.
- WHO could come up with concrete recommendations based on the WHO/OECD/Health Canada meeting of October 2000 for developing a system that would be widely applicable and practical.
- The surveillance system/WHO should be informed of any syndrome or infection thought to be contracted from xenotransplantation.
- The IAEA could be approached for funding for international support of assays involving radioisotopes.
- WHO could identify countries in which xenotransplantation occurs.
- WHO could develop a recommendation for biological specimen archives to be developed as part of any surveillance programme.
- WHO could compile a database including numbers and types of xenotransplantation performed in Member States.
- WHO could conduct and publish in the World Health Report a survey of where xenotransplantation occurs, to include a rigorous quantitative estimate of xenotransplantation events in each country.
- WHO could develop general recommendations for obtaining informed consent in situations that may represent a risk to the general public.
- WHO could explore how/whether informed consent procedures could be adapted for the circumstances of xenotransplantation, including obtaining consent from close patient contacts and the acceptance of the need to comply with subsequent monitoring and follow-up.

General discussion – Summary of consensus points

There was consensus that there was a need to act internationally in advance of clinical evidence demonstrating the success of xenotransplantation to ensure that "guidelines are in place as soon as possible". In view of the continuing shortage of allografts, xenograft organ and tissue transplants have the potential for providing "an unlimited supply" of organs and, if the approach is proven successful, may be rapidly and widely used. It will be important to "proceed with caution" since the potential health gains are very significant but are balanced against the potential health risks. There is thus a need for more research, surveillance and oversight. A cautionary note was expressed by some that xenotransplantation is an expensive, high technology endeavour, that will be accessible to only some rather than to many and that it thus has the potential to "widen the gap" between the affluent and the poor nations.

There was consensus that WHO could play a significant role by providing leadership to facilitate global networking and cooperation and could consider the following:

- Encourage nations to support consensus on basic principles for xenotransplantation safety and oversight.
- Identify countries in which xenotransplantation occurs and support the approach that regulation must be in place in all countries in which clinical trials of xenotransplantation occur.
- Develop general recommendations for obtaining informed consent in situations that may represent a risk to the general public and in which individual rights and public good may come into conflict.
- Develop and encourage nations to support agreement to monitor and control travel of recipients for xenotransplantation.
- Implement an international xenotransplantation surveillance network as previously discussed.

International regulation of human tissues and cells for transplantation

Breakout group report

Human cells and tissues provide benefits to patients which, to meet their needs, must be provided through ethical processes which maximize access, equity and safety. It was felt that:

- WHO could promote discussion between regulators to create an agreed definition of cells and tissues and to provide model regulatory framework options for Member States.
- WHO could provide guiding principles for the transparent regulation of ethical, organizational and technical aspects of tissue and cell transplantation, in order to increase both access and safety for patients.
- WHO could advocate the development of sustainable models of regulation, capacity building, training and surveillance, facilitating regional and global cooperation.
- In the current context of increasing commercialization of cell and tissue transplantation, the existence of the trafficking of tissues on a global basis is of increasing concern.
- In the interests of patient care, the innovation of high quality and sustainable delivery of evidence-based therapy requires consideration of the following issues: efficacy, quality, safety, collection, processing, storage, distribution, tissue exchange, access, equity, commercial 'for-profit' organizations, sustainability of 'not-for-profit' government and charitable organizations, research and innovation, education and training, import and export, similarities of autologous and allogeneic tissues, traceability, respect for donor rights, donor consent, donor payments, market regulation and market surveillance.

General discussion – Summary of consensus points

- The volume and complexity of activity in the tissue and cell transplantation sectors are rising rapidly and thus need to be taken into account by WHO guidelines.

- There is a need for uniformity and agreement on harmonization of definitions of "tissue".
- There is a need to consider ways in which to increase corneal transplantation in the developing world with the resolution of quality issues since anecdotal reports include failure rates of up to 50%.
- Problems in tissue banking and transplantation include:
  - Poor levels of education, training and research in tissue banking globally.
  - Inconsistent approaches to donor consent.
  - Limited or non-existent evidence for efficacy of transplantation of some tissues.
  - Unregulated commercialization.
  - Inability to provide "origin to destiny" traceability of tissues.
  - Lack of harmonization of regulatory standards delivering high costs for tissue banks.
  - Concern about ensuring self-sustainability of "not-for-profit banks" on the one hand while preventing excessive income of "for-profit banks" in the context of altruistically-donated human material.
- WHO can provide leadership to facilitate global networking, cooperation and international data exchange on the therapeutic use of human tissues.
- WHO's roles in corneal donation could include advocacy, support in identifying relevant needs and support for capacity building.
- Harmonization of the international regulation of haematopoietic stem cells is critical to continued global interchange of HLA-matched donations.
- Protection of patient opportunity should be achieved through global communication between regulators and providers, development of global professional standards, registration of serious donor adverse events and the continuous measurement and publication of transplant outcomes.
- WHO has potential roles to facilitate communication, maintain global networking and sustain cooperation between regulators and providers of haematopoietic stem cells.

Approach to developing transplantation programmes

Breakout group report

The group focused on the ways in which WHO can assist countries with developing national programmes in transplantation, as well as helping with evaluation and monitoring of programmes once they are in place.

Assessing needs: WHO could provide countries with the data on the magnitude of the problem related to the specificities of the country and the needs and available human and financial resources.

Realistic objectives: WHO could help countries to define objectives of the programme, taking into account affordability and sustainability, e.g. the cost of establishing tissue banks and facilitating the use of generic drugs for immunosuppression following kidney transplants.

Better coordination: This would involve WHO in improving international coordination amongst institutes who have similar goals.

Defining resources: The group sees a role for WHO in helping countries to develop local resources through technical collaboration, networking, promoting pilot and regional projects, helping with training fellowships and workshops to facilitate transfer of technologies.

Access to transplantation: WHO could encourage governments to develop protocols that promote equitable access to transplantation in their populations.

General discussion – Summary of consensus points

- Several aspects of the 1991 Guiding Principles have been contradicted by contemporary transplantation practices and attitudes, thus defining the need to consider revision of the Guiding Principles.
- Clinical transplantation has expanded considerably in the past 15 years, raising wider and more complex technical and ethical issues that must be addressed.
- There was unanimous support for the need of a WHO Expert Advisory Panel for transplantation.
- There is considerable global disparity and diversity in the level and extent of government regulation and oversight of both donation and transplantation of organs and tissues.
- There is an agreed need to have global safety and quality principles for the regulation of organs and tissues.
- Prevention of renal disease is by far the most cost-effective approach to population health but will not succeed in eliminating the need for kidney transplantation.
- There is a need to identify and disseminate the information on successful "models" of transplantation that use local resources and cultural norms. Success will not come from the provision of isolated components of support but should involve the comprehensive support of individuals and programmes extending throughout legal, social and clinical aspects of transplant programmes. The creation of such comprehensive "alliances" between institutions can be promoted by the approval and help of transplantation societies, governments and WHO.
- Funding of new transplantation programmes must be sustainable and inclusive of long term drug costs.
- A national transplantation agency constitutes a possible model for effective integrated development of donation and transplantation.
- The regulation of health tourism is a relevant strategy to inhibit illegal organ trafficking.
- WHO could facilitate alliances and cooperation between Member States, professional associations, industry associations and regulatory authorities at legal, ethical and technical levels.
- WHO may assist development of agreement on minimum datasets needed to support evidence-based transplant and allocation policies.

Closure of the meeting and closing remarks

The host, the Minister of Health and Consumer Affairs of Spain, Dr A.M. Pastor Julián, thanked the members of the meeting for their participation. She emphasized that from an ethical perspective the most important achievement is to ensure that access to transplantation is governed by conditions of equity. She highlighted the evident need for all countries to have at their disposal a suitable legal framework that covers the removal of organs and tissue, their processing and implantation. She encouraged all to think on a global scale and act on a local scale respecting and making use of socioeconomic and political factors. She concluded that all are very well aware of the need to combat any kind of trade in human body parts and that the most effective way to do this is to provide quality treatment to patients in all countries within a framework of equity and equality.

WORLD HEALTH ORGANIZATION

Ethics, access and safety in tissue and organ transplantation: Issues of global concern

Madrid, Spain, 6-9 October 2003,

Programme of Work

Monday, 6 October

09:30 **Opening session**

- Welcome and introduction — Ministry of Health of Spain (Blanca Miranda)
- Welcome and introduction — WHO (Alex Capron)
- Introduction of participants
- General information
- Comments on the agenda
- Election of chairpersons and rapporteurs

10:30 **Session 1 – Introduction and general objectives of the conference**

- WHO and transplantation — Luc Noël
- Objectives of the meeting and method of work — Nikola Biller-Andorno

10:45 **Session 2 – Global activity and developments in transplantation**

- Organ transplantation — Carl-Gustav Groth
- Tissue transplantation — Rüdiger von Versen

11:30 *Coffee break*

12:00
- Cell transplantation — Jeremy Chapman
- Xenotransplantation — Eda Bloom

13:00 *Lunch*

14:30 **Session 3 – Current challenges and normative issues**

- The 1991 Guiding Principles: Roots and implications — Alex Capron
- Current ethical issues in transplantation — Nikola Biller-Andorno
- Need for government oversight and role WHO — Luc Noël

Discussion

15:30 **Session 4 – Deceased donors**

– Access to organs	Blanca Miranda
– Prior consent of deceased and family permission	Diego Garcia

16:30 *Coffee break*

Brief presentations:
Japan's organ transplantation policy and the necessity for comparative study (Tsutomu Iuchi)
Consent of deceased donors in Latin American legislation (Adelio Misseroni Raddatz)
Deceased donors: Access to organs (Carlos Soratti)
Paucity of deceased donor kidneys: A sociocultural issue (Farhat Moazam)
Decision-making on organ donation in the Republic of Korea: The deceased donor and the brain-dead donor (Kyu-Won Jung)
Deceased donors (Ashok Shah)

Discussion

18:00 *Recess*

Tuesday, 7 October

09:00 **Summary and messages from the previous day**

09:30 **Session 5 – Living donors**

– Safety of the living donor: Informed consent	Frank Delmonico
– Incentives and disincentives in organ donation	Leo de Castro
– Global justice and the traffic in human organs	Nancy Scheper-Hughes

Brief presentations:
Indian scenario (Kanjaksha Ghosh)
Organ vending and trafficking (Abdallah Daar)

Discussion

11:30 *Coffee break*

12:00 **Session 6 – Tissue processing and banking**

– Issues in tissue banking and transplantation	Yongyudh Vajaradul
– Haematopoietic stem cell transplantation	Jeremy Chapman

Brief presentations:
Haematopoietic stem cell transplantation in India (Kanjaksha Ghosh)
Issues in tissue banking and transplantation in Japan/Quality management system (Naoshi Shinozaki)
Special concerns in haematopoietic stem cell transplantation (Carlos Soratti)
Issues in tissue banking and transplantation (Eda Bloom)

13:00 *Lunch*

14:30 **Session 7 – Quality and safety in the process of transplantation**

– Basic requirements for organ transplantation	Ryota Shirakura
– Core technical principles in transplantation	Laura St Martin
– Canadian national standards for all transplantation	Paul Dubord

Brief presentations:
Brazil (José Antônio de Faria Vilaça)
Good practices for tissue banking (Eda Bloom)
Egypt (Ibrahim Badran)

16:00 *Tea break*

16:30 **Session 8 – Xenotransplantation**

– Safety and availability of xenotransplantation	Abdallah Daar
– National and regional policies/USA perspective/ Overview	Eda Bloom

Brief presentations:
Safety/informed consent and education (Eda Bloom)
Council of Europe (Karl-Friedrich Bopp)
Safety and availability of xenotransplantation (Tadahito Kanda)
Regulatory oversight in Canada (Maura Ricketts)

Discussion

18:00 *Recess*

Wednesday, 8 October

09:00 **Summary and messages from the previous day**

09:30 **Session 9 – Efficacy, access and allocation**

– Pakistan and live renal transplantation: Moral dimensions of access and allocation	Farhat Moazam
– Impact of international collaboration	Esmeralda Luciolli/ Driss Zaïd
– Cornea banking in East Africa	Ashok Shah

Brief presentations:
Evidence-based transplantation policy development (Laura St Martin)
South Africa (Nettie Mbatha)
Perspective in transplantation: Senegal (Boucar Diouf)
Russia (Nikolai Tarabarko)

11:30 *Coffee break*

12:00 **Session 10 – Regulation and government oversight of transplantation**

– Difficulty in defining and achieving safety in the EU	Bernard Loty
– Legal response to transplantation in South Korea	Kyu-Won Jung

Brief presentations:
The need for government oversight and the role of WHO (Carlos Soratti)
Mexico (Aturo Dib-Kuri)
Regulation of transplantation in Colombia (Klaus Mieth)
European Union policy on blood, tissues, cells and organs (Eduardo Fernandez-Zincke)

Discussion

13:00 *Lunch*

14:30 **Breakout** Groups – Round tables: Developing agendas for further action

- Procurement of organs and tissues from deceased donors
- Living organ donor programmes
- Xenotransplantation
- International regulation of human tissues and cells for transplantation
- Developing transplantation: Matching needs and resources

16:00 *Tea break*

16:30 **General discussion**

18:00 *Recess*

Thursday, 9 October

09:00 **Summary and messages from the previous day**

09:30 **Closing session – Sorting out the issues and the way forward**

11:00 *Coffee break*

11:30 **Closure of the meeting**

Closing speech given by Dra A.M. Pastor Julián, Minister of Health of Spain

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