

Human Tissue Research and Clinical Practice

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ABSTRACT

Clinical practice and medical research have made tremendous advances in the past 40 years. Organ transplantation has become established in mainstream medical treatment. Legislation has been modified to cater for the need for donor organs to facilitate this form of treatment for patients with organ failure. The next major step is in stem cell research and the potential benefits for the treatment of degenerative conditions. Singapore has been grappling with these issues and has produced guidelines for the conduct of this research. Ethical consideration and legislation need to keep up with these advances, so as to be compatible with the majority cultural and religious affiliations of Singaporeans.

Keywords: human tissue research, medical ethics and legislation in Singapore, stem cells

INTRODUCTION

Both clinical practice and medical research is advancing at a rapid rate, in order to attempt to refine diagnosis, treatment and survival of the human race. At the SingHealth Research Network Forum on 27 to 28 February 2004, speakers consistently showed how scientific and technological advances have, and can be, used for a variety of clinical situations to improve outcomes. These range from the detection of disease, with genetic counselling and appropriate pre-natal DNA testing, to analysing the effects of biochemical and metabolic changes in tissues of degenerative conditions. How can and do, we regulate this research and subsequent clinical implementation? Singapore is grappling with this as are many countries with similar medical advances. Medical ethics and legislation need to keep up with both scientific advancement and changes in community attitudes. Statutory regulations now have to encompass older issues like tissue donation and organ transplantation, and recent ones like gene therapy and cloning.

The aim of this paper is to initiate thought-provoking discussion on ethical issues relevant to our daily clinical practices. After all, the developments we shall face may not be that distant. Many of us can still remember the heated debates of 1978, when Steptoe and Edwards

carried out the first successful in-vitro fertilisation, which has made a big difference to the lives of many infertile couples.

HUMAN TISSUE RESEARCH

Regenerative tissue is defined as tissue that, after injury or removal, is replaced in the body of a living person by natural processes of growth or repair (for example, bone marrow or skin) while non-regenerative tissue are organs like the kidneys, liver, lungs and heart. This distinction is useful as organ transplantation is now well established and Singapore has introduced new legislation for this. Stem cell research, however, is pushing the frontiers of the application of ethical principles in medicine. I shall use these 2 broad areas for further discussion.

The *Human Organ Transplant (Amendment) Bill (HOTA)* was passed by the Singapore Parliament on 6 January 2004. These amendments allow for the extension of organ donation beyond the kidneys to the heart, liver and cornea. The Bill extended organ donation from death due to accidents to all causes of death where tissue is likely to be viable, for example, sudden intracranial haemorrhage. All Singapore citizens and Permanent Residents between the ages of 21 and 60 years are included under HOTA. People can opt out

if they object to having their organs removed upon death. Prior authorisation from the relevant Transplant Ethics Committees is required before a living donor organ transplant can proceed. Individuals not covered by HOTA, such as Muslims, can opt in for organ transplantations under the *Medical Therapy, Education and Research Act (MTERA)*. Muslims are not automatically included under HOTA because once a Muslim person dies, his body belongs to his relatives and they have the right to over rule his/her rights to pledge their organs. The Islamic Religious Council of Singapore has encouraged Muslims to pledge their organs on an opt-in basis with permission of their next-of-kin (waris) and 1 other witness.

As organ transplantation is now well established, the 2 main ethical boundaries are the extent to which voluntary donation is encouraged in the community and the new areas of organ transplantation like the pancreas and brain. The Singapore Government has chosen the pathway of some other industrialised countries to donation, with the opt-out system in order to meet the needs of organ failure patients. The recent extension of the Act, from kidneys to hearts, livers and corneas is compatible with reproducible success in these transplantations. Other organs like the lungs, may be included in due course based on local and international success with this procedure.¹

STEM CELL RESEARCH AND ETHICAL CONSIDERATIONS FOR SINGAPORE

In Singapore, we see the whole spectrum of degenerative conditions that lead to significant disability and death. These include neurological conditions like cerebral infarctions, Parkinson's disease and neurodegenerative conditions of the spine and muscles; endocrine-related conditions with significant end-organ damage like diabetes mellitus; myocardial infarctions and other vascular occlusive conditions that lead to loss of function of the organ; and autoimmune diseases that have life-threatening effects on major organ functions in the body. Any new experimental treatment for these conditions needs to lead to an assessment of the effectiveness of the treatment balanced against potential side-effects. While this assessment includes research on new pharmaceutical drugs, research on embryonic stem cells raises the barrier. Ethical conflict will exist between destructive embryo research and the tremendous potential benefits for the individual and the community at large.

The use of bone marrow and solid organ transplantations has been in place for almost a generation. While its place in medical management has been established, there are cultural, religious and social

issues that prevent its widespread accessibility. Nevertheless, the process involves informed consent from both the donors and the recipients. Stem cells can be harvested from embryos, fetuses and adults. A foetus, however, cannot give informed consent and obtaining foetal tissue from elective termination of pregnancies is unacceptable in certain religious circles, especially when the foetus is considered a living being.

Pluripotent embryonic stem cells can give rise to useful cell types found in the adult body. Sources of this include primordial germ cells developing in foetal tissue and from unwanted early pre-implantation embryos not used for the treatment of infertility. If any of these cells are used to produce immortal cell lines, ethical issues arise further in the confidentiality and economic value of these cell lines. Does the donor have any recompense to the economic value of the cell lines produced from their cells or from their unused pre-implantation embryos? If this line is widely made available, can the genetic information remain anonymous? What are the implications if individuals donate cells for financial benefit?

Life is continuous from the individual sperm and egg cells to the multi-celled fertilised embryo, to the developing foetus. When morally does life actually start, when killing embryos to obtain stem cells is not perceived as murder? Does a set time limit of 14 days, which is deemed the time just before the foetus begins to form and tissue differentiation occurs, as is the law in some countries, seem acceptable to the community at large? Can regulation be brought in retrospectively so that established cell lines are destroyed or prospectively so that certain cell lines can be used as they had already been in existence at the time of regulation? Does regulation that affects one country apply to another so that research on human embryonic stem cell lines is done on those cell lines imported from other countries? Finally, when stem cells are used for the treatment of degenerative conditions, would it remain a realistic clinical option for the rich only? This form of treatment will remain labour intensive and expensive although potential exists for gene modification that will allow larger production of these cells.

The use of adult stem cells may circumvent some of the issues presented above. Its use, however, may have limitations in the treatment of some degenerative conditions where embryonic stem cells are more effective in correcting the pathological processes present. The use of somatic cell nuclear transfer — where a somatic cell nucleus is transferred into a donated oocyte, from which the nuclear material has been removed — may for some overcome ethical

barriers. This is if the entity is considered an artifact and not an embryo, defined as the product of fusion between a sperm and an egg. This process, however, may also have restricted use in clinical practice because of the cost involved and the transfer of genetic material from an older nucleus as opposed to an embryonic one.

Any legislation that incorporates community values and views on stem cell research and clinical treatment has to make allowances for future changes in community attitudes and cultures. We have seen this in the use of organ donation and transplantation leading to the new and evolving regulations in Singapore.

The community needs to be educated in the value of ongoing research as well as the potential benefits and pitfalls of this research. It is not uncommon for Asian populations to be reluctant to support medical research if it involves the donation of blood or tissues, even if this donation may be useful for them in the future. Michael Wood from the Mayo Foundation has stated that “top level input and direction in creating national health care policy is not only the privilege of the medical profession but also a distinct responsibility”.² He suggested 3 areas where physician leadership is emerging in crafting health care policy, local institutional governance and health care institutional management. I would like to add that as healthcare professionals, we need to be actively involved and act as leaders in patient and community education so that ethical issues like stem cell research is openly discussed and that regulations are not implemented by representatives of society without reflecting medical and societal opinions.

In December 2000, the Singapore Government appointed the Bioethics Advisory Committee (BAC) to examine issues arising from biomedical research and development, incorporating ethical, social and legal issues, in Singapore. This will also allow biomedical researchers to collaborate with researchers from countries that not only have already put into place ethical and legal protocols, but also require them from other countries as well. The Committee saw its main objective as to “balance two key ethical commitments: protection of human life and the rights and welfare of the individual, and to advance human life by curing disease”.

SPECIFIC ISSUES FOR HEALTH PROFESSIONALS AND RESEARCHERS

Appropriate care and consideration is made for the collection and banking of tissue for research. While “tissue banking” as a structured and organised

collection of tissues has been performed for more than 100 years, current experimental techniques allow more than just histological diagnosis of the tissues obtained. Current recommendations from the BAC emphasise that research on tissues taken from both live patients and pathological archival collections, regardless of the fact that this may have been taken for diagnostic or therapeutic reasons, need to be reclassified as part of a research tissue bank with appropriate regulations and supervision by Institutional Ethics Committees. It is important that this is adhered to, as useful developments from research on these tissues are then not blocked because of the lack of relevant ethics and legal approvals. However, the use of leftover tissue (surplus to clinical requirements) for biomedical research and the ownership of that tissue is still open to debate. Each individual situation has to be reviewed accordingly so as not to prejudice the rights of the patient and that of the greater public good. For example, the discovery of human immunodeficiency virus in stored human tissues after the AIDS epidemic surfaced had allowed both basic scientists and epidemiologists to identify potential sources and spread of the virus over time.

In addition to Institutional Review Boards (IRBs), the BAC has recommended setting up a statutory authority to license, control and monitor all human stem cell research in Singapore. This is important for supervising and enforcing the ethical and legal direction for the conduct of all human stem cell research and “level the field for researchers across hospital, academic and private institutions”. This may also allow cross-fertilisation of ideas so that local collaborations can be set up. The other role of this authority would be to coordinate changes in legal and ethical situations based on changes in scientific knowledge, medical treatment and societal values and take into consideration accepted international consensus on relevant legal and ethical principles. As stated in the BAC recommendations, when research projects transcend national borders, “countries may demand proof of each other that there is equivalence in the degree of ethical and legal protection or regulation of human tissue research in order to allow the cross-frontier transfer of research data for collaboration”.³

One of the major local issues I believe is that of obtaining consent. The BAC has stated that “full, free and informed consent is the cornerstone of the legal and ethical legitimacy and validity of a gift of human tissue intended for research”.⁴ Training should be organised as to the best way to obtain consent and present information to the patient. I believe public forums presenting state-of-the-art human tissue and

stem cell research need to be done regularly so that the local population realise the value of this research to them and their descendants. Singaporeans have diseases with a genetic and environmental basis like people from the rest of the world. World-class treatment involves the use of not only the latest pharmaceutical agents, but also particular operative procedures, cellular, tissue or organ transplantations. Reticence in providing informed consent and therefore tissue donation may stem from ignorance. This could be overcome with both general public awareness and specific family educational programmes. Reassurance of confidentiality of information obtained is crucial to obtaining the confidence of the public, specific patients and their families. Training in methods of obtaining informed consent with sufficient flexibility to adapt to each situation, will allow more successful donations under current guidelines and future legislation.

REPRODUCTIVE CLONING

The BAC has recommended “a complete ban on the implantation of a human embryo created by the application of cloning technology into a womb, or any treatment of such an embryo intended to result in its development into a viable infant”.⁵ Two South Korean researchers have recently cloned human embryos for culling to extract stem cells for research. These same 2 researchers have called for a global ban on reproductive cloning. How do we reconcile the production of human embryos purely to be sacrificed for their cells? Are we to accept that this is reasonable on the basis that the cloned embryos are “artifacts” and not a product of cellular fusion? The concern is that the same technology that has produced these embryos will be used to produce cloned human beings.

What is to stop researchers from providing cloned embryos for human beings wealthy enough to sponsor that research for their own gains? The BAC has allowed the creation of human embryos specifically for research if it satisfies 3 criteria:

1. there is strong scientific merit in, and potential medical benefit from, such research
2. no acceptable alternative exists
3. this is done on a highly selective case-by-case basis, with specific approval from the proposed national statutory board

This recommendation, while fair, should still be open to debate so that guidelines are strictly drawn up to define the validity of this research.

SUMMARY

Organ transplantation and stem cell research are both here to stay. As healthcare professionals, we each have the responsibility to be aware of the advances, keep up with potential and real therapeutic benefits, and understand the ethical principles and legislation that encompass these areas.

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