A revived opportunity for fetal research

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One of President Bill Clinton's early decisions was to lift the ban on federally supported research on human fetal tissue. Under what circumstances can research on this material be justified?

DURING the four decades that have followed the US Supreme Court's landmark Roe vs Wade decision, the debate over abortion has intensified to the point of ferocity, culminating recently in the murder of an obstetrician. Much of the effort of the anti-abortion movement has been directed against clinicians and against researchers working on fetal tissue. Thirty years ago, a national commission chaired by Kenneth Ryan produced guidelines for research on living human fetuses. The Ryan commission assumed that the tissues of dead fetuses would be treated precisely like those of any dead individual, under the terms of the Anatomical Gift Act.

Indeed, dead fetal tissue did not become a subject of contention until 1988 when the first results of treatment of people with Parkinson's disease using fetal adrenal glands were announced. In the minds of 'right-to-life' adherents, the reports conjured up the image of a massive abortion market fuelled by the need for fetal parts. The Bush administration responded by prohibiting the use of dead fetal tissues for research of any kind in institutions supported by federal funds. Now that the Clinton administration has swiftly and decisively reversed the ban, the time is right to discuss the scientifically and ethically appropriate uses of this material.

We believe that the use of discarded fetal tissue for research and/or therapy should be to increase knowledge of human development and/or improvement of the human condition. Acknowledgement of the unique and non-trivial nature of the material should be mandatory. The review panels now assembling to evaluate research proposals must ensure that human material is essential, and animal or substitute models should be used for preference when possible.

Although pre-implantation conceptuses and zygotes fertilized *ex utero* have contributed to our understanding of phenomena occurring during early human embryogenesis, aborted fetal tissues are more available and so provide new opportunities for clinical research, which if encouraging will stimulate more basic research in human development. What are these opportunities?

Human development

Relatively little is known about the cellular events dictating differentiation in humans. The use of fetal tissue can provide insights, for example the characterization last year[1] of two distinct subsets of pluripotent stem cells from human fetal bone marrow. Individual fetal cells with specific immunophenotypes were found to differentiate either into haematopoietic precursors or into the stromal cells capable of supporting them. The work, if confirmed, could eventually lead to clinical application in the treatment of aplastic anaemia and malignancy. Other research should help to show why the fetus is particularly susceptible to human teratogens.

Detailed study of placentation, fetal organs and physiology can now be more easily related to human development. Of particular interest is the occurrence of confined chorionic mosaicism, a condition in which the fetal karyotype is discordant with the placenta, which has been described in 1 per cent of cases of chorionic villus sampling performed for prenatal cytogenetic diagnosis[2]. Fetal trisomy with subsequent selective chromosome loss has already been demonstrated to have significant effects on fetal well-being[3], and may be the initiating step in the development of disorders associated with uniparental disomy[4]. Material obtained from terminated fetuses will allow cytogenetic and molecular characterization of the relationships between the fetus and its extra-embryonic tissues, contributing to an understanding of events preceding various clinically recognized conditions.

Human therapy

Although the transplantation of fetal neuronal tissue into the basal ganglia of patients suffering from Parkinson's disease has received media attention, the potential for fetal cells to act as a vector for gene-transfer therapy will probably have a more significant long-term impact. Retrovirus-mediated gene transfer into transplantable cells has been proposed for several conditions, but treatment of immunodeficiency caused by adenosine deaminase (ADA) deficiency appears imminent. Transfer of the human ADA gene into haematopoietic stem-cell precursors has been achieved in murine models[5], and long-term expression of the transplanted human ADA gene in rhesus monkeys has now been demonstrated[6].

Fetal cells are inherently preferable to their adult equivalents for transplantation because they are immunologically immature and retain the ability to proliferate. Fetal material is transplantable either as an organ or as a cellular suspension. Cellular transplantation can be performed either pre- or postnatally, the techniques are straightforward, cells can be manipulated in culture, and there is the possibility of extended storage by cryopreservation[7]. In France, haematopoietic stem cells derived from human fetal livers (7–12 weeks' gestation) have been transplanted into four unrelated second- and third-trimester fetuses with inherited immunodeficiencies or haemoglobinopathies. In three of the four cases, engraftment was successful, resulting in amelioration of symptoms[8].

Human fetal tissue has already been used to treat disorders ranging from inborn errors of metabolism to neurodegenerative diseases for all age groups. In France, fetal liver transplantation has been performed for the past 16 years, with encouraging, if preliminary, results[9]. There are improvements in patients with advanced Parkinson's disease who received human fetal ventral mesencephalic implants[10–12]. Experiments can now be designed systematically to study factors related to the clinical success of these transplants. The results are likely to have application in a range of degenerative disorders. □

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