PONTIFICAL ACADEMY FOR LIFE

DECLARATION ON THE PRODUCTION AND THE SCIENTIFIC AND THERAPEUTIC USE OF HUMAN EMBRYONIC STEM CELLS

This document seeks to contribute to the debate on the production and use of *embryonic stem cells* which is now taking place in scientific and ethical literature and in public opinion. Given the growing relevance of the debate on the limits and liceity of the production and use of such cells, there is a pressing need to reflect on the ethical implications which are present.

The first section will very briefly set out the most recent scientific data on stem cells and the biotechnological data on their production and use. The second section will draw attention to the more relevant ethical problems raised by these new discoveries and their applications.

Scientific Aspects

Although some aspects need to be studied more thoroughly, a commonly accepted *definition* of Astem cell" describes it as a cell with two characteristics: 1) the *property of an unlimited self-maintenance* - that is, the ability to reproduce itself over a long period of time without becoming differentiated; and 2) the *capability to produce non-permanent progenitor cells*, with limited capacity for proliferation, from which derive *a variety of lineages of highly differentiated cells* (neural cells, muscle cells, blood cells, etc.). For about thirty years stem cells have provided a vast field of research in adult tissue,[i][i] in embryonic tissue and in *in vitro* cultures of embryonic stem cells of experimental animals.[ii][ii] But public attention has recently increased with a new milestone that has been reached: the production of human embryonic stem cells.

Human embryonic stem cells

Today, the *preparation of human embryonic stem cells* (human ES cells) implies the following[iii][iii]: 1) the *production of human embryos* and/or the *use* of the surplus embryos resulting from *in vitro* fertilization or of frozen embryos; 2) the *development* of these embryos to the stage of initial blastocysts; 3) the *isolation* of the embryoblast or inner cell mass (ICM) - which implies the *destruction of the embryo*; 4) *culturing* these cells on a feeder layer of irradiated mouse embryonic fibroblasts in a suitable medium, where they can multiply and coalesce to form colonies; 5) repeated *subculturing* of these colonies, which lead to the formation of *cell lines* capable of multiplying indefinitely while preserving the characteristics of ES cells for months and years.

These ES cells, however, are only the point of departure for the preparation of *differentiated cell lines*, that is, of cells with the characteristics proper of the various tissues (muscle, neural, epithelial, haematic, germinal, etc.). Methods for obtaining them are still being studied;[iv][iv] but the injection of human ES cells into experimental animals (mice) or their culture *in vitro* in controlled environments to their confluence have shown that they are able to produce differentiated cells which, in a normal development, would derive from the three different

embryonic tissue layers: endoderm (intestinal epithelium), mesoderm (cartilage, bone, smooth and striated muscle) and ectoderm (neural epithelium, squamous epithelium).[v][v]

The results of these experiments had a great impact on the world of both science and biotechnology - especially medicine and pharmacology - no less than the world of business and the mass media. There were high hopes that the application of this knowledge would lead to new and safer ways of treating serious diseases, something which had been sought for years.[vi][vi] But the impact was greatest in the political world.[vii][vii] In the United States in particular, in response to the long-standing opposition of Congress to the use of federal funds for research in which human embryos were destroyed, there came strong pressure from the National Institutes of Health (NIH), among others, to obtain funds for at least using stem cells produced by private groups; there came also recommendations from the National Bioethics Advisory Committee (NBAC), established by the Federal Government to study the problem, that public money should be given not only for research on embryonic stem cells but also for producing them. Indeed, persistent efforts are being made to rescind definitively the present legal ban on the use of federal funds for research on human embryos.

Similar pressures are being brought to bear also in England, Japan and Australia.

Therapeutic cloning

It had become clear that the therapeutic use of ES cells, as such, entailed significant risks, since - as had been observed in experiments on mice - tumours resulted. It would have been necessary therefore to prepare specialized lines of *differentiated cells* as they were needed; and it did not appear that this could be done in a short period of time. But, even if successful, it would have been very difficult to be certain that the inoculation or therapeutic implant was free of stem cells, which would entail the corresponding risks. Moreover there would have been a need for further treatment to overcome immunological incompatibility. For these reasons, three methods of *therapeutic cloning*[viii][viii] were proposed, suitable for preparing pluripotent human embryonic stem cells with well defined genetic information from which desired differentiation would then follow.

1. *The replacement of the nucleus of an oocyte with the nucleus of an adult cell of a given subject*, followed by embryonic development to the stage of blastocyst and the use of the inner cell mass (ICM) in order to obtain ES cells and, from these, the desired differentiated cells.

2. *The transfer of a nucleus of a cell of a given subject into an oocite of another animal.* An eventual success in this procedure should lead - it is presumed - to the development of a human embryo, to be used as in the preceding case.

3. *The reprogramming of the nucleus of a cell of a given subject by fusing the ES cytoplast with a somatic cell karyoplast, thus obtaining a "cybrid"*. This is a possibility which is still under study. In any event, this method too would seem to demand a prior preparation of ES cells from human embryos.

Current scientific research is looking to the first of these possibilities as the preferred method, but it is obvious that - from a moral point of view, as we shall see - all three proposed solutions are unacceptable.

Adult stem cells

From studies on adult stem cells (ASC) in the last thirty years it had been clearly shown that many adult tissues contain stem cells, but stem cells capable of producing only cells proper to a given tissue. That is, it was not thought that these cells could be reprogrammed. In more recent years,[ix][ix] however, *pluripotent stem cells* were also discovered in various human tissues - in bone marrow (HSCs), in the brain (NSCs), in the mesenchyme (MSCs) of various organs, and in umbilical cord blood (P/CB, placental/cord blood); these are cells capable of producing different types of cells, mostly blood cells, muscle cells and neural cells. It was learnt how to recognize them, select them, maintain them in development, and induce them to form different types of mature cells by means of growth factors and other regulating proteins. Indeed noteworthy progress has already been made in the experimental field, applying the most advanced methods of genetic engineering and molecular biology in analyzing the genetic programme at work in stem cells,[x][x] and in importing the desired genes into stem cells or progenitor cells which, when implanted, are able to restore specific functions to damaged tissue.[xi][xi] It is sufficient to mention, on the basis of the reported references, that in human beings the stem cells of bone marrow, from which the different lines of blood cells are formed, have as their marker the molecule CD34; and that, when purified, these cells are able to restore entirely the normal blood count in patients who receive ablative doses of radiation and chemotherapy, and this with a speed which is in proportion to the quantity of cells used. Furthermore, there are already indications on how to guide the development of neural stem cells (NSCs) through the use of various proteins - among them neuroregulin and bone morphogenetic protein 2 (BMP2) - which can direct NSCs to become neurons or glia (myelin-producing neural support cells) or even smooth muscle tissue.

The note of satisfaction, albeit cautious, with which many of the cited works conclude is an indication of the great promise that Aadult stem cells" offer for effective treatment of many pathologies. Thus the affirmation made by D. J. Watt and G. E. Jones: A The muscle stem cell, whether it be of the embryonic myoblast lineage, or of the adult satellite status, may well turn out to be a cell with far greater importance to tissues other than its tissue of origin and may well hold the key to future therapies for diseases other than those of a myogenic nature" (p. 93). As J. A. Nolta and D. B. Kohn emphasize: AProgress in the use of gene transfer into haemotopoietic cells has led to initial clinical trials. Information developed by these early efforts will be used to guide future developments. Ultimately, gene therapy may allow a number of genetic and acquired diseases to be treated, without the current complications from bone marrow transplantation with allogeneic cells." (p. 460); and the confirmation offered by D. L. Clarke and J. Frisén: "These studies suggest that stem cells in different adult tissues may be more similar than previously thought and perhaps in some cases have a developmental repertoire close to that of ES cells" (p. 1663) and Ademonstrates that an adult neural stem cell has a very broad developmental capacity and may potentially be used to generate a variety of cell types for transplantation in different diseases@ (p. 1660).

The progress and results obtained in the field of adult stem cells (ASC) show not only their great plasticity but also their many possible uses, in all likelihood no different from those of embryonic stem cells, since plasticity depends in large part upon genetic information, which can be reprogrammed.

Obviously, it is not yet possible to compare the therapeutic results obtained and obtainable using embryonic stem cells and adult stem cells. For the latter, various pharmaceutical firms are already conducting clinical experiments[xii][xii] which are showing success and raising genuine hopes for the not too distant future. With embryonic stem cells, even if various experimental approaches prove positive,[xiii][xiii] their application in the clinical field - owing precisely to the serious ethical and legal problems which arise - needs to be seriously reconsidered and requires a great sense of responsibility before the dignity of every human being.

Ethical Problems

Given the nature of this article, the key ethical problems implied by these new technologies are presented briefly, with an indication of the responses which emerge from a careful consideration of the human subject from the moment of conception. It is this consideration which underlies the position affirmed and put forth by the Magisterium of the Church.

The ***first ethical problem***, which is fundamental, can be formulated thus: *Is it morally licit to produce and/or use living human embryos for the preparation of ES cells?*

The answer is negative, for the following reasons:

1. On the basis of a complete biological analysis, the living human embryo is - from the moment of the union of the gametes - a *human subject* with a well defined identity, which from that point begins its own *coordinated, continuous and gradual development*, such that at no later stage can it be considered as a simple mass of cells.[xiv][xiv]

2. From this it follows that as a A*human individual*" it has the *right* to its own life; and therefore every intervention which is not in favour of the embryo is an act which violates that right. Moral theology has always taught that in the case of A*jus certum tertii*" the system of probabilism does not apply.[xv][xv]

3. Therefore, the ablation of the inner cell mass (ICM) of the blastocyst, which critically and irremediably damages the human embryo, curtailing its development, is a *gravely immoral* act and consequently is *gravely illicit.*

4. *No end believed to be good*, such as the use of stem cells for the preparation of other differentiated cells to be used in what look to be promising therapeutic procedures, *can justify an intervention of this kind.* A good end does not make right an action which in itself is wrong.

5. For Catholics, this position is explicitly confirmed by the Magisterium of the Church which, in the Encyclical *Evangelium Vitae*, with reference to the Instruction *Donum Vitae* of the Congregation for the Doctrine of the Faith, affirms: AThe Church has always taught and

continues to teach that the result of human procreation, from the first moment of its existence, must be guaranteed that unconditional respect which is morally due to the human being in his or her totality and unity in body and spirit: >The human being is to be respected and treated as a person from the moment of conception; and therefore from that same moment his rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life'"(No. 60).[xvi][xvi]

The ***second ethical problem*** can be formulated thus: *Is it morally licit to engage in so-called Atherapeutic cloning*" by producing cloned human embryos and then destroying them in order to produce ES cells?

The answer is negative, for the following reason: Every type of therapeutic cloning, which implies producing human embryos and then destroying them in order to obtain stem cells, is illicit; for there is present the ethical problem examined above, which can only be answered in the negative.[xvii][xvii]

The ***third ethical problem*** can be formulated thus: *Is it morally licit to use ES cells, and the differentiated cells obtained from them, which are supplied by other researchers or are commercially obtainable?*

The answer is negative, since: prescinding from the participation - formal or otherwise - in the morally illicit intention of the principal agent, the case in question entails a proximate material cooperation in the production and manipulation of human embryos on the part of those producing or supplying them.

In conclusion, it is not hard to see the seriousness and gravity of the ethical problem posed by the desire to extend to the field of human research the production and/or use of human embryos, even from an humanitarian perspective.

The possibility, now confirmed, of using ***adult stem cells*** to attain the same goals as would be sought with embryonic stem cells - even if many further steps in both areas are necessary before clear and conclusive results are obtained - indicates that adult stem cells represent a more reasonable and human method for making correct and sound progress in this new field of research and in the therapeutic applications which it promises. These applications are undoubtedly a source of great hope for a significant number of suffering people.

The President
Prof. Juan de Dios Vial Correa

The Vice President
S.E. Mons. Elio Sgreccia

Vatican City, August 25, 2000.

NOTES

i [i].Cf. M. LOEFFLER, C. S POTTEN, *Stem Cells and Cellular Pedigrees - a Conceptual Introduction*, in C. S. POTTEN (ed.), *Stem Cells*, Academic Press, London (1997), pp.1-27; D. Van der KOOY, S. WEISS, *Why Stem Cells?*, Science 2000, 287, 1439-1441.

ii [ii].Cf. T: NAKANO, H. KODAMA, T. HONJO, *Generation of Lymphohematopoietic Cells from Embryonic Stem Cells in Culture*, Science 1994, 265, 1098-1101; G. KELLER, *In Vitro Differentiation of Embryonic Stem Cells*, Current Opinion in Cell Biology 1995, 7, 862-869; S. ROBERTSON, M. KENNEDY, G. KELLER, *Hematopoietic Commitment During Embryogenesis*, Annals of the New York Academy of Sciences 1999, 872, 9-16.

iii [iii].Cf. J. A .THOMSON, J. ITSKOVITZ-ELDOR, S. S. SHAPIRO et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, Science 1998, 282, 1145-1147; G. VOGEL, *Harnessing the Power of Stem Cells*, Science 1999, 283, 1432-1434.

iii [iv].Cf. F. M. WATT, B. L. M. HOGAN, *Out of Eden: Stem Cells and Their Niches*, Science 2000, 287, 1427-1430.

v [v].Cf. J. A. THOMSON, J. ITSKOVITZ-ELDOR, S. S. SHAPIRO et al., *op. cit*.

vi [vi].Cf. U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, *Neural Grafting: Repairing the Brain and Spinal Cord*, OTA-BA-462, Washington, DC, U.S. Government Printing Office, 1990; A. McLAREN, *Stem Cells: Golden Opportunities with Ethical Baggage*, Science 2000, 288, 1778.

vii [vii].Cf. E. MARSHALL, *A Versatile Cell Line Raises Scientific Hopes, Legal Questions*, Science 1998, 282, 1014-1015; J. GEARHART, *New Potential for Human Embryonic Stem Cells*, ibid., 1061-1062; E. MARSHALL, *Britain Urged to Expand Embryo Studies*, ibid., 2167-2168; 73 SCIENTISTS, *Science Over Politics*, Science 1999, 283, 1849-1850; E. MARSHALL, *Ethicists Back Stem Cell Research, White House Treads Cautiously*, Science 1999, 285, 502; H. T. SHAPIRO, *Ethical Dilemmas and Stem Cell Research*, ibid., 2065; G. VOGEL, *NIH Sets Rules for Funding Embryonic Stem Cell Research*, Science 1999, 286, 2050; G. KELLER, H. R. SNODGRASS, *Human Embryonic Stem Cells: the Future Is Now*, Nature Medicine 1999, 5, 151-152; G.J. ANNAS, A. CAPLAN, S. ELIAS, *Stem Cell Politics, Ethics and Medical Progress*, ibid., 1339-1341; G. VOGEL, *Company Gets Rights to Cloned Human Embryos*, Science 2000, 287, 559; D. NORMILE, *Report Would Open Up Research in Japan*, ibid., 949; M. S. FRANKEL, *In Search of Stem Cell Policy*, ibid., 1397; D. PERRY, *Patients Voices: the Powerful Sound in the Stem Cell Debate*, ibid., 1423; N. LENOIR, *Europe Confronts the Embryonic Stem Cell Research Challenge*, ibid., 1425-1427; F. E. YOUNG, *A Time for Restraint*, ibid., 1424; EDITORIAL, *Stem Cells*, Nature Medicine 2000, 6, 231.

viii [viii].D. DAVOR, J. GEARHART, *Putting Stem Cells to Work*, Science 1999, 283, 1468-1470.

ix [ix].Cf. C. S. POTTEN (ed.), *Stem Cells*, Academic Press, London 1997, p. 474; D. ORLIC, T. A. BOCK, L. KANZ, *Hemopoietic Stem Cells: Biology and Transplantation*, Ann. N. Y. Acad. Sciences, vol. 872, New York 1999, p. 405; M. F. PITTENGER, A. M. MACKAY, S.C. BECK et al., *Multilineage Potential of Adult Human Mesenchymal Stem Cells*, Science 1999, 284, 143-147; C. R. R. BJORNSON, R.L. RIETZE, B. A. REYNOLDS et al., *Turning Brain into Blood: a Hematopoietic Fate Adopted by Adult Neural Stem Cells* in vivo, Science 1999, 283, 534-536; V. OUREDNIK, J. OUREDNIK, K. I. PARK, E. Y. SNYDER, *Neural Stem Cells - a Versatile Tool for Cell Replacement and Gene Therapy in the Central Nervous System*, Clinical Genetics 1999, 56, 267-278; I. LEMISCHKA, *Searching for Stem Cell Regulatory Molecules: Some General Thoughts and Possible Approaches*, Ann. N.Y. Acad. Sci. 1999, 872, 274-288; H. H. GAGE, *Mammalian Neural Stem Cells*, Science 2000, 287, 1433-1438; D. L. CLARKE, C. B. JOHANSSON, J. FRISEN et al., *Generalized Potential of Adult Neural Stem Cells*, Science 2000, 288, 1660-1663; G. VOGEL, *Brain Cells Reveal Surprising Versatility*, ibid., 1559-1561.

x [x].Cf. R. L. PHILLIPS, R. E. ERNST, I. R. LEMISCHKA, et al., *The Genetic Program of Hematopoietic Stem Cells*, Science 2000, 288, 1635-1640.

xi [xi].Cf. D. J. WATT, G. E. JONES, *Skeletal Muscle Stem Cells: Function and Potential Role in Therapy*, in C. S. POTTEN, *Stem Cells*, *op. cit*., 75-98; J. A. NOLTA, D. B. KOHN, *Haematopoietic Stem Cells for Gene Therapy*, ibid., 447-460; Y. REISNER, E. BACHAR-LUSTIG, H-W. LI et al., *The Role of Megadose CD34+ Progenitor Cells in the Treatment of Leukemia Patients Without a Matched Donor and in Tolerance Induction for Organ Transplantation*, Ann. N.Y. Acad. Sci. 1999, 872, 336-350; D. W. EMERY, G. STAMATOY-ANNOPOULOS, *Stem Cell Gene Therapy for the ß-Chain Hemoglobinopathies*, ibid., 94-108; M. GRIFFITH, R. OSBORNE, R. MUNGER, *Functional Human Corneal Equivalents Constructed from Cell Lines*, Science 1999, 286, 2169-2172; N. S. ROY, S. WANG, L. JIANG et al., In vitro *Neurogenesis by Progenitor Cells Isolated from the Adult Hippocampus*, Nature Medicine 2000, 6, 271-277; M. NOBLE, *Can Neural Stem Cells Be Used as Therapeutic Vehicles in the Treatment of Brain Tumors?*, ibid., 369-370; I. L. WEISSMAN, *Translating Stem and Progenitor Cell Biology to the Clinic: Barriers and Opportunities*, Science 2000, 287, 1442-1446; P. SERUP, *Panning for Pancreatic Stem Cells*, Nature Genetics 2000, 25, 134-135.

xii [xii].E. MARSHALL, *The Business of Stem Cells*, Science 2000, 287, 1419-1421.

xiii [xiii].Cf. O. BRUSTLE, K. N. JONES, R. D. LEARISH et al., *Embryonic Stem Cell-Derived Glial Precursors: a Source of Myelinating Transplants*, Science 1999, 285, 754-756; J. W. McDONALD, X-Z LIU, Y. QU et al., *Transplanted Embryonic Stem Cells Survive, Differentiate and Promote Recovery in Injured Rat Spinal Cord*, Nature Medicine 1999, 5, 1410-1412.

xiv [xiv].Cf. A. SERRA , R. COLOMBO, *Identità e Statuto dell'Embrione Umano: il Contributo della Biologia*, in PONTIFICIA ACADEMIA PRO VITA, *Identità e Statuto dell'Embrione Umano*, Libreria Editrice Vaticana, Città del Vaticano 1998, pp.106-158.

xv [xv].Cf. I. CARRASCO de PAULA, *Il Rispetto Dovuto all'Embrione Umano: Prospettiva Storico-Dottrinale*, in ibid., pp. 9-33; R. LUCAS LUCAS, *Statuto Antropologico dell'Embrione Umano*, in ibid., pp.159-185; M. COZZOLI, *L'Embrione Umano: Aspetti Etico-Normativi*, in ibid., pp.237- 273; L. EUSEBI, *La Tutela dell'Embrione Umano: Profili Giuridici*, in ibid., pp. 274-286.

xvi [xvi].JOHN PAUL II, *Encyclical Letter "Evangelium Vitae"* (25 March 1995), Acta Apostolicae Sedis 1995, 87, 401-522; cf. also CONGREGATION FOR THE DOCTRINE OF THE FAITH, *Instruction on Respect for Human Life in Its Origins and on the Dignity of Procreation "Donum Vitae"* (22 February 1987), Acta Apostolicae Sedis 1988, 80, 70-102.

xvii [xvii].CONGREGATION FOR THE DOCTRINE OF THE FAITH, *op. cit*., I, no. 6; C.B.COHEN (ed.), *Special Issue: Ethics and the Cloning of Human Embryos*, Kennedy Institute of Ethics Journal 1994, n.4, 187-282; H. T. SHAPIRO, *Ethical and Policy Issues of Human Cloning*, Science 1997, 277, 195-196; M.L. DI PIETRO, *Dalla Clonazione Animale alla Clonazione dell'Uomo?*, Medicina e Morale 1997, no. 6, 1099-2005; A. SERRA, *Verso la Clonazione dell'Uomo? Una Nuova Frontiera della Scienza*, La Civiltà Cattolica 1998 I, 224-234; ibid., *La Clonazione Umana in Prospettiva "Sapienziale"*, ibid., 329-339.