Pontifical Academy for Life

Study Group on

BANKS OF UMBILICAL CORD BLOOD

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Book cover: Vera Kratochvil - *Mother kissing her baby daughter*

Contents

INTRODUCTION

Until a few years ago, the umbilical cord, once it had been detached, became a part of biological refuse. Scientific interest in the umbilical cord arose towards the end of the '80s, in connection with the perfecting of the techniques for marrow transplants on the one hand and the discovery of haematopoietic stem cells in the umbilical cord on the other.

Towards the end of the '60s, the acquisition of new knowledge about the functioning of the histo-compatibility system *human leucocyte antigen* (HLA) had made possible the first successes in the transplantation of allogeneic bone marrow in patients affected by severe immune-deficiency.[1] In 1969 Edward Donnall Thomas, when he established the '*Seattle bone marrow transplant team'* had in fact introduced bone marrow transplantation into clinical practice, which was put at the service both of patients being treated for cancer or for leukaemia and of patients affected by haematological pathologies or by severe immune-deficiency. In 1988, to bone marrow transplantation there was added the possibility of transplanting autologous or allogeneic haematopoietic stem cells, obtained by removing them from peripheral circulation.[2] Allogeneic-type transplants, then as now, present the difficulty, of no minor clinical significance, of the immunological compatibility between the donor and the recipient; it is estimated that about two-thirds of patients awaiting transplant of haematopoietic stem cells cannot find a compatible donor.

The discovery of haematopoietic progenitor cells in umbilical cord blood, therefore, aroused great expectations among researchers and among clinicians. Besides, the capacity that was demonstrated for cord blood cells to withstand well the procedures of cryo-preservation has made it possible, practically, for them to be used, at first, in

1 Gatti R.A., Meuwissen H.J., Allen H.D., Hong R., Good R.A., Immunological *reconstitution of sex-linked lymphopenic immunological deficiency*, The Lancet 1968; 2(7583): 1366-1368.

2 Kessinger A., Armitage J.O., Landmark J.D., Smith D.M., Weisenburger D.D., *Autologous peripheral stem cell transplantation restores haematopoietic function following marrow ablative therapy*, Science 1988; 71(3): 723-727.

children needing haematopoietic reconstitution.[3] The first attempt at transplanting haematopoietic stem cells derived from the umbilical cord goes back to 1972[4], while the first clinical success was reported in 1988 by Eliane Gluckman[5], for the treatment of a five year old child affected by a severe form of Fanconi's anaemia. Recently, the discovery has been made of other types of stem cells, barely differentiated, (mesenchymal stem cells[6], endothelial progenitor cells[7], pluripotent simil-embryonic cells[8]), broadening the range of therapeutic applications which can be hypothesised, in particular in the field of regenerative medicine.[9] These successes have increased further scientific interest in relation to the umbilical cord and, at the same time, as is happening increasingly with successes in medicine, had fed the expectations of public opinion, that is of those who may become the next to benefit from such successes. It is probable, also in the case of cord stem cells, that announcements of new therapies have run ahead of practical reality, expanding the gap between the expectations of patients and clinical reality. This makes all the more necessary for there to have a proper dissemination of accurate

3 Broxmeyer H.E., Douglas G.W., Hangoc G., Cooper S., Bard J., English D., Arny M., Thomas L., Booyse E.A., *Human umbilical cord blood as a potential source of transplantable haematopoietic stem/ progenitor cells*, Proceedings of the National Academy of Sciences of the United States of America 1989; 86(10): 3828-3832.

4 Ende M., Ende N., *Hematopoietic transplantation by means of fetal (cord) blood. A new Method*, Virginia Medical Monthly 1972; 99(3): 276-280.

5 Gluckman E., Broxmeyer H.A., Auerbach A.D., Friedman H.S., Douglas G.W., Devergie A., Esperou H., Thierry D., Socie G., Lehn P., *Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical cord blood from an HLA-identical sibling*, The New England Journal of Medicine 1989; 321(17): 1174-1178.

6 Flynn A., Barry F., O'Brien T., *UC blood-derived mesenchymal stromal cells, an overview*, Cytotherapy 2007; 9(8): 717-726.

7 Bompais H., Chagraoui J., Canron X., Crisan M., Liu X.H., Anjo A., Toll-Le Port C., Leboeuf M., Charbord P., Bikfalvi A., Uzan G., *Human endothelial cells derived from circulating progenitors display specific functional properties compared with mature vessel wall endothelial cells*, Blood 2004; 103(7): 2277-2584.

8 McGuckin C.P., Forraz N., Baradez M.O., Navran S., Zhao J., Urban R., Tilton R., Denner S., *Production of stem cells with embryonic characteristics from human umbilical cord*, Cell Proliferation 2005; 38(4): 245-255.

9 Reimann V., Creutzig U., Kögler G., *Stem cells derived from cord blood in transplantation and regenerative medicine*, Deutsches Ärzteblatt International 2009; 106(50): 831-836.

information in this field, both on the part of experts and on the part of those who are potentially the intended beneficiaries of these therapies.

Alongside the perspectives of clinical use, the technical possibility of preserving umbilical cord blood has fostered the development at present of so-called cord blood banks. In the space of about thirty years, we have witnessed a vast flowering of these structures in almost all parts of the world. As with all things which enjoy such rapid development, practice advances far ahead of regulation, so that, inevitably, we have reached the point where public regulation has become necessary, to ensure that such realities are integrated effectively and efficaciously within the social fabric within which they operate, in the service of the common good. Banks of umbilical cord blood arise from the union between an act of individual solidarity (on the part of subjects who donate cord blood for therapeutic purposes or for research) and the possibilities offered by medical science and technology, which make possible the preservation and the eventual use of that which, until a few decades ago, was considered waste biological material, but which today is becoming more and more a most valuable form of biological material for research and for clinical medicine.

At a distance of thirty years since the birth of the first cord bank, basically, the main issue which has to be faced is of an ethical-social nature and, in the first place, it concerns whether or not it would be right to invest a certain level of resources in associations presently in existence for the preservation of cord blood by way of these 'banks'. Together with this aspect, a matter of immediate significance is the need to define the ways in which cord banks operate, for the purpose of ensuring that being at the service of individuals, the spirit on the basis of which all medical activity and all scientific research advances, will always be fostered as the priority. The issue which stands out today as obvious in the sight of everyone, in fact, is that not only private banks, but also public banks may move away from the spirit of solidarity, which impels people to donate cord blood, to undertake their actions for the purposes of profit, such that the act of donation would be manipulated and that there would be discrimination at the social level, in relation to the distribution of the therapeutic benefits offered by the use of cord blood cells.

The relevance of the ethical-social issue linked to the creation of cord blood banks and the urgency with which this issue is invested has led the Pontifical Academy for Life to set up a study group with the objective of defining scientific aspects, ethical aspects and questions of regulation linked to this theme. The meeting between experts in groups and with other consultors has also led to the emergence, in the course of the studies, of the relevance of the "precocious clamping" of the umbilical cord (also as the source of a potential conflict of interests) as a procedure required or at least preferable, for the purpose of obtaining cord blood with "optimal" characteristics in terms of its preservation and of its eventual use. Since the precise terms of this question are still being debated, it has been decided to refer to it in a section apart (Appendix).

The members of the study group are: Prof. Alfredo Anzani, professor of Bioethics at the *University of San Rafaele* in Milan (Italy), Prof. Justo Aznar, Director of the *Institute of Life Sciences of the Catholic University of Valencia* (Spain), Prof. Monica Lopez Barahona, Director of the *Centre for Bio-Health Studies* in Madrid (Spain), Prof. Carlo Casini, President of the *Pro-Life Movement* (Italy), Rev. Prof. Maurizio Faggioni, Professor of Bioethics at the *Academy of St. Alphonsus* (Roma), Prof. Eliane Gluckman, President of *Eurocord* and President of the *European School of Haematology*, Prof. Lukas Kenner, Professor of Molecular Pathology at the *Medical University* of Vienna (Austria), Prof. Colin McGuckin, President of the *Institute of Research into Cellular Therapy* in Lyon (France), Prof. Carlo Petrini, the person responsible for the *Bioethics Unit of the Higher Institute of Health* (Rome), Mons. Jacques Suaudeau, study assistant at the *Pontifical Academy for Life* (Vatican City).

The study group is coordinated by Prof. Salvatore Mancuso, Ordinary Professor of Obstetrics and Gynaecology, formerly Director of the *Department for the Protection of the Health of Women and of Unborn Life at the Catholic University of the Sacred Heart* (Rome).

A specific contribution in relation to the question of precocious clamping was made by Prof. Jose Luis Diaz-Rosello, *Neo-natal Department* of the University Hospital of Montevideo (Uruguay).

MEDICAL SCIENTIFIC ASPECTS

I. TYPES OF STEM CELLS PRESENT IN THE BLOOD OF THE UMBILICAL CORD.

Different types of stem cells are contained in the blood of the umbilical cord[10]: haemapoetic stem cells, mesenchymal stem cells and progenitor endothelial cells. At present cord blood cells have 1) a clinical application for hematologic purposes; 2) a prospect of use in the context of regenerative medicine.

Haematopoetic Stem Cells.[11] Initially, in 1974, S. Knudtzon[12] demonstrated the existence of mature haematopoetic stem cells in the blood of the umbilical cord, while about ten years further on M. Ogawa and collaborators[13] demonstrated the existence of primitive progenitor haemapoetic cells. On the basis of these studies umbilical cord blood has been recognised as a rich source of haematopoetic stem

10 Stem cells are progenitor cells with a high potential for proliferation, capable of self-renewal (i.e., able of producing daughter cells equal to themselves) and of generating more than on specialised cells types (totipotent stem cells are capable of giving rise to all the specialised cells which constitute the various tissues and organs). A fundamental role seems to be played by the so-called "niche", i.e., by the micro-environment of the stem cell in situ: such a micro-environment would maintain the cells in their state of stemness, by mean so biochemical signals which inhibit their maturation. In man four sources of stem cells have been identified so far: 1) embryonic stem cells (derived from the inner mass of the blastocysts); 2) germ cells derived from the foetus; 3) stem cells from the umbilical cords; 4) "adult" or "somatic" stem cells (identified in all tissues of the adult organism, such as bone marrow, pancreas, bone, cartilage, liver, skin, nervous system and fat tissue).

11 Haematopoetic stem cells are cells which are able to give rise to all the cellular elements of peripheral blood (red blood cells, white blood cells and platelets). These cells are able to regenerate the cellular content of the bone in all those cases in which it has been damaged as a result of pathologies, accidental exposure to ionising radiation or chemo-radio-therapy treatment for cancer. They are present in the bone marrow (where they constitute 1-3% of the cell population present), in peripheral blood (0.01-0.1%) and in cord blood (0.1-0.4%).

12 Knudtzon S., *In vitro growth of granulocyte colonies from circulating cells in human cord blood*, Blood 1974; 43, (3): 357-361.

13 Nakahata T., Ogawa M., *Hematopoietic colony-forming cells in umbilical cord blood with extensive capability to generate mono- and multipotential hematopoietic progenitors*, The Journal of Clinical Investigation 1982; 70(6): 1324-1328. Leary A.G., Ogawa N., *Blast cell colony assay for umbilical cord blood and adult bone marrow progenitors*, Blood 1987; 69(3): 953-956.

cells. Numerous other studies have demonstrated that such cells are capable of reproducing haematopoesis in vitro and can be preserved by freezing.[14] The wealth of stem cells in umbilical cord blood explains very well, from a scientific point of view, their efficacy in the treatment of haematological diseases.

Mesenchymal Stem Cells.[15] Their presence has initially been suggested from the discovery of a therapeutic potential of cord blood beyond its haematopoetic effect.[16] Cord blood, in fact, offers an excellent alternative to bone marrow as a source of mesenchymal stem cells[17]. Such cells have been studied in depth in comparison with the mesenchymal stem cells of bone marrow and it has emerged that, while being morphologically and immunologically similar to the latter, they present a greater versatility for differentiation, being capable of giving rise to cells proper to the mesoderm (osteocytes, chondrocytes, adipocytes, skeletal myoblatsts), of the neuro-ectoderm (neuron and glia) and of the endoderm (hepatocytes).[18] The presence of mesenchymal stem cells has been demonstrated also in Wharton's jelly (the mucoid connective tissue which support the two arteries and the vein within the umbilical cord and which, until now, has been considered as a tissue without any use): such cells have been differentiated in osteoblasts, chondrocytes, adipocytes, hepatocytes and in cells producing insulin.[19]

14 Knudtzon S., *In vitro growth of granulocytic colonies from circulating cells in human cord blood*, Blood 1974; 43 (3): 357-361. Fauser A.A., Messner H.A., *Granuloerythrooietic colonies in human bone marrow, peripheral blood and cord blood*, Blood 1978; 52(6): 1243-1248. Prindull G., Prindull B., Meulen N., *Haematopoietic stem cells (CFUc) in human cord blood*, Acta Paediatrica Scandinavica 1978; 67(4): 413-416. Broxmeyer H.E., Douglas G.W., Hangoc G., Cooper S., Bard J., English D., Arny M., Thomas L., Booyse E.A., *Human umbilical cord blood as a potential source of transplantable haematopoietic stem/progenitor cells*, Proceedings of the National Academy of Sciences of the United States of America 1989; 86 (10): 3828-3832. Broxmeyer H.E., Hangoc G., Cooper S., Ribeiro R.C., Graves V., Yoder M., Wagner J., Vadhan-Raj S., Benninger L., Rubinstein P., *Growth characteristics and expansion of human umbilical cord blood and estimation of its potential for transplantation in adults*, Proceedings of the National Academy of Science of the United States of America 1992; 89(9): 4109-4113.

15 Mesenchymal stem cells are cells which are able to give rise to fat, cartilage and bone tissue. They are contained inside the medullary stroma. They constitute a population of pluripotent cells, so that, if they are properly directed, they can given rise to cells with the characteristics of various tissues.

16 Bieback K., Klüter H., *Mesenchymal stromal cells from umbilical cord blood*, Current Stem Cell Research and Therapy 2007; 2(4): 310-323.

17 In umbilical cord blood the mesenchymal cells are found in a form as yet immature, which we could define as 'pre-mesenchymal'. The presence of cells with these characteristics in the developing foetus is important because they constitute a reserve tank of cells which are then distributed to the various organs or are used in the repair of damaged cells or in the development of the immune system. Properly mesenchymal cells are to be found, instead, in Wharton's gelatine.

18 Flynn A., Barry F., O'Brien T., *UC blood-derived mesenchymal stromal cells: an overview*, Cytotherapy 2007; 9(8): 717-726. Hou L., Cao H., Wang D., Wei G., Bai C., Zhang Y., Pei X., *Induction of umbilical cord blood mesenchymal stem cells into neuron-like cells in vitro*, International Journal of Hematology 2003; 78(3): 256-261. Lee O.K., Kuo T.K., Cheng W-M, Lee K.D., Hsieh S.L., Chen T.H., *Isolation of multipotent mesenchymal stem cells from umbilical cord blood*, Blood 2004; 103(5): 1669-1675. Goodwin H.S., Bickenese A.R., Chien S.N., Bogucki B.D., Oliver D.A., Quinn C.O., Wall D.A., *Multilineage Differentiation Activity by Cells Isolated From Umbilical Cord Blood: Expression of Bone, Fat, and Neural Markers*, Biology of Blood and Marrow Transplantation 2001; 7(11): 581-588. Rosada C., Justensen J., Melsvik D., Ebbbesen P., Kassem M., *The human umbilical cord blood; a potential source for osteoblasts progenitor cells*, Calcified Tissue International 2003; 72(2): 135-142. Lee O.K., Kuo T.K., Cheng W.M., Lee K.D., Hsieh S.L., Chen T.H., *Isolation of multipotent mesenchymal stem cells from umbilical cord blood*, Blood 2004; 103(5): 1669-1675. Wang J.F., Wang L.J., Wu Y.F., Xiang Y., Xie C.G., Jia B.B., Harrington J., McNiece I.K., *Mesenchymal stem/progenitor cells in human umbilical cord blood as support for* ex vivo *expansion of CD34+ hematopoietic stem cells and for chondrogenic differentiation*, Haematologica 2004; 89(7): 837-844. Gang E.J., Jeong J.A., Hong S.H., Hwang S.H., Kim S.W., Yang I.H., Ahn C., Han H., Kim H., *Skeletal Myogenic Differentiation of Mesenchymal Stem Cells Isolated from Human Umbilical Cord Blood*, Stem Cells 2004; 22(4): 617-624. Bicknese A.R., Goodwin H.S., Quinn C.O., Henderson V.C., Chien S.N., Wall D.A., *Human umbilical cord blood cells can be induced to express markers for neurons and glia*, Cell Transplantation 2002; 11(3): 261-264.

19 Wang H.S., Hung S.C., Peng S.T., Huang C.C., Wei H.M., Guo Y.J., Fu Y.S., Lai M.C., Chen C.C., *Mesenchymal Stem Cells in the Wharton's Jelly of the Human Umbilical Cord*, Stem Cells 2004; 22(7): 1330-1337. Zhang Y.N., Lie P.C., Wei X., *Differentiation of mesenchymal stromal cells derived from umbilical cord Wharton's jelly into hepatocyte-like cells*, Cytotherapy 2009; 11(5): 548-558. Wu L.F., Wang N.N., Liu Y.S., Wei X., *Differentiation of Wharton's jelly primitive stromal cells into insulin-producing cells in comparison with bone marrow mesenchchymal stem cells*, Tissue Engineering 2009; 15(10): 2865-2873.

Endothelial Progenitor Cells.[20] Also present in umbilical cord blood these cells contribute to the haematopoetic environment. According to some researchers, such cells could play a role in angiogenetic therapy and in endothelisation of transplanted bio-engineered tissues.[21]

Besides, some research is being directed towards the study of cells of the immune system, in view of their possible application in the context of immuno-therapy and in the diagnostic forecasting of certain diseases.[22]

One relevant characteristic of cord blood stem cells is that they are young (the length of their telomeres is relatively long) and immature. Different groups of researchers, using a cell depletion technology have recently isolated from human cord blood some pluripotent stem cells very similar to embryonic stem cells, in a way which can be reproduced and in significant quantities.[23] Some other researchers have found a specific type of pluripotent stem cells derived from umbilical cord blood that they named USSCs (*unrestricted somatic stem cells*).[24]

20 Endothelial progenitor cells are stem cells originating in the marrow, involved in the repair of the endothelial and in angiogenesis.

21 Wu K.H., Zhou B., Lu S.H., Feng B., Yang S.G., Du W.T., Gu D.S., Han Z.C., Liu Y.L., *In vitro and in vivo differentiation of human umbilical cord derived stem cells into endothelial cells*, Journal of Cell Biology 2007; 100(3): 608-616.

22 Kim Y.J., Broxmeyer H.E., *Immune regulatory cells in umbilical cord blood and their potential roles in transplantation tolerance*, Crrit Rev Oncol Hematol 2011; 79(2): 112-26.

23 McGuckin C.P., Forraz N., Baradez M.O., Navran S., Zhao J., Urban R., Tilton R., Denner S., *Production of stem cells with embryonic characteristics from human umbilical cord*, Cell Proliferation 2005; 38(4): 245-255. Sun B., Roh K.H., Lee S.R., Lee Y.S., Kang K.S., *Induction of human umbilical cord blood-derived stem cells with embryonic stem cell phenotypes into insulin producing islet-like structure*, Biochemical and Biophysical Research Communications 2007; 354(4): 919-923. McGuckin C., Jurga M., Ali H., Strbad M., Forraz N., *Culture of embryonic stem cells from human umbilical cord blood and onward differentiation to neural cells in vitro*, Nature Protocols 2008; 3(6): 1046-1055.

24 Kögler G., Sensken S., Airey J.A., Trapp T., Müschen M., Feldhahn N., Liedtke S., Sorg R.V., Fischer J., Rosenbaum C., Greschat S., Knipper A., Bender J., Degistirici O., Gao J., Caplan A.J., Colletti E.J., Almeida-Porada G., Müller H.W., Zanjani E., Wernet P., *A new human somatic stem cell from placental blood with intrinsic pluripotent differentiation potential*, The Journal of Experimental Medicine 2004; 200(2): 123-135. Kögler G., Sensken S., Wernet P., *Comparative generation and characterization of pluripotent unrestricted somatic cells with mesenchymal stem cells from human cord blood*, Experimental Hematology 2006; 34(11): 1589-1595.

II. THE CLINICAL USE OF UMBILICAL STEM CELLS

Clinical application for hematologic purposes. As far as the clinical use of stem cells from cord blood is concerned, this has turned out to be relevant above all in the haematological setting. After the first efforts of Ende & Ende and of Gluckman,[25] there has been a growing interest in respect of blood from the umbilical cord as an alternative source of progenitor haematopoetic cells for transplant. In principle, cord blood stem cells transplants can be used in all clinical conditions, in paediatric patients or in adults, who require the substitution of blood or of the immune system (reconstitution of bone marrow after chemotherapy for lymphoma or leukaemia; haemoglobinopathy of genetic origin, such as sickle-cell disease and thalassemia; genetic diseases bearing upon the immune system, such as severe combined immunodeficiencies (SCID) caused for example by adenosine deanimase deficiency (ADA-SCID); some types of anaemia or marrow aplasia, such as Falconi's anaemia; Diamond Blackfran anaemia; and some metabolic diseases). The interest of using cord blood stems instead of haematopoietic stem cells comes from a significantly lower incidence of GVHD (graft versus host disease) with cord blood stem cells, presumably linked to the 'naive' condition of the immune system of cord blood, permitting its use also in the case of HLA discordance. J.E. Wagner, examining the results of 23 transplants of cord blood in 1994, with or without HLA compatibility, did not encounter in the series any case of acute transplant illness.[26] Also in 1994 J. Kurtzberg and collaborators

25 In 1972 Ende & Ende reported the first attempt at the transplant of cord stem cells (cfr. Ende M., Ende N., *Hematopoietic transplantation by means of fetal (cord) blood. A new Method*, Virginia Medical Monthly 1972; 99(3): 276-280), whereas the first clinical success was reported by E. Gluckman e coll. In Paris in 1988, into a five-year old child affected by a serious form of Fanconi's anaemia. In this case Gluckman used the cord blood of a brother of the patient, with identical HLA (cfr. Gluckman E., Broxmeyer H.A., Auerbach A.D., Friedman H.S., Douglas G.W., Devergie A., Esperou H., Thierry D., Socie G., Lehn P., *Hematopietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling*, The New England Journal of Medicine 1989; 321(17): 1174-1178.

26 Wagner J.E., *Umbilical Cord Blood Transplantation: Overview of the Clinical Experience*, Blood Cells 1994; 20(2/3): 227-234.

demonstrated that transplants of cord blood from donors without kinship connections with the recipient and, on this basis, having only a partial HLA compatibility, had given positive results.[27] Numerous other studies subsequently confirmed the possibility of using cord blood from HLA discordant donors, without bonds of kinship to the recipient, with the purpose of ensuring haematopoetic reconstitution after myeloablative treatment.[28]

In fact, nowadays, cord blood transplantation is used ever more frequently in children and in adults with neoplastic malignancies, in particular with acute leukaemia, who require a allogeneic transplant of haematopoetic stem cells and who do not have a compatible donor among their relatives (*unrelated cord blood transplant*).[29] However, allogeneic transplantation of cord blood is equally just as valid an alternative source of haematopoetic stem cells for transplant to adults affected by malignant haematological diseases and who do not have the benefit of a HLA compatible donor from among their relatives. Furthermore, in the face of equivalent clinical results, the transplantation of blood cord stem cells offers the advantage of quicker availability in the case of urgency, apart from the greater ease of finding a suitable donor. The speed of integration of the transplanted cells into the recipient organism is slower in the case of cord blood transplants by comparison with bone marrow transplants;

27 Kurtzberg J., Graham M., Casey J., Olson J., Stevens C.E., Rubinstein P., *The use of umbilical cord blood in mismatched related and unrelated hemopoietic stem cell transplantation*, Blood Cells 1994; 20(2/3): 275-283.

28 Wagner J.E., Rosenthal J., Sweetman R., Shu X.O., Davies S.M., Ramsay N.K., McGlave P.B., Sender L., Cairo M.S., *Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: analysis of engraftment and acute graft-versus-host disease*, Blood 1996; 88(3): 795-802. Thomson B.G., Robertson K.A., Gowan D., Heilman D., Broxmeyer H.E., Emanuel D., Kotylo P., Brahmi Z., Smith F.O., *Analysis of engraftment, graft-versus-host disease, and immune recovery following unrelated donor cord blood transplantation*, Blood 2000; 96(8): 2703-2711.

29 Gluckman E., Rocha V., *Indications and results of cord blood transplant in children with leukemia*, Bone Marrow Transplantation 2008; 41(Suppl.2): S80-S82. Arcese W., Rocha V., Labopin M., Sanz G., Iori A.P., de Lima M., Sirvent A., Busca A., Asano S., Ionescu I., Wernet P., Gluckman E., *Unrelated cord blood transplants in adults with hematologic malignancies*, Haematologica 2006; 91(2): 223-230.

nevertheless, this disadvantage is counter-balanced by a lower incidence of serious transplant disease (transplant versus host). Overall, however, the success of the transplant depends to a great extent upon the quality of the umbilical cord (number of stem cells) and the degree of compatibility between the cord and the recipient. In particular, it is recommended to select units of cord blood with more than $3x10^7$ of nucleated cells/Kg or with $2x10^5$ of CD4+/Kg.[30] Above all, since 2004, the transplant of cord blood, for a long time reserved only to children because of the relatively small quantity of haematopoetic cells contained in the cord blood, has seen a notable increase in its use also in the adult, thanks above all to the development of clinical protocols allowing the use of two or even three units of different cord blood in one and the same patient.

Prospect of use in the context of regenerative medicine. Another promising development is the possible clinical use in relation to regenerative medicine, although at present this is still at the experimental and/or clinical trial stage. The main difficulty arises from the fact that, apart from progenitor endothelial stem cells, the other non haematopoetic cells are rare in cord blood and their presence is not to be found in all samples of umbilical cord blood. In animal models, such cells seems promising for the treatment of ictus and cerebral trauma (the intra-venous administration of umbilical cord blood improves neurological deficit and reduces lesions,[31] probably thanks also to

30 Gluckman E., Rocha V., *Cord blood tranplantation: state of the art*, Haematologica 2009; 94(4): 451-454. Locatelli F., *Improving cord blood transplantation in children*, British Journal of Haematology 2009; 147(2): 217-226.

31 Lu D., Sanberg P.R., Mahmood A., Li Y., Wang L., Sanchez-Ramos J., Chopp M., *Intravenous administration of human umbilical cord blood reduces neurological deficit in the rat after traumatic brain injury*, Cell Transplantation 2002; 11(3): 275-281. Liao W., Xie J., Zhong J., Liu Y., Du L., Zhou B., Xu J., Liu O., Yang S., Wang J., Han Z., Han Z.C., *Therapeutic effect of human umbilical cord multipotent mesenchymal stromal cells in a rat model of stroke*, Transplantation 2009; 87(3): 350-359. Liao W., Zhong J., Yu J., Xie J., Liu Y., Du L., Yang S., Liu P., Xu J., Wang J., Han Z., Han Z.C., *Therapeutic benefit of human umbilical cord derived mesenchymal stromal cells in intracerebral hemorrhage rat: implications of anti-inflammation and angiogenesis*, Cell Physiol Biochem 2009; 24(3-4): 307-316.

an anti-inflammatory and angiogenetic action[32]), for the treatment of some neuro-degenerative diseases, such as Parkinson's disease and Huntington's disease, diseases for which at present there exists only symptomatic treatment (the cord stem cells are able to initiate and to sustain the process of repairing the nerve tissues damaged by the disease[33]), for the treatment of lateral amyotrophic sclerosis (the infusion of mononucleate cells of human cord blood increases the survival of animal models in a way which depends upon the quantity of cells injected[34]), for the treatment of spinal cord lesions (improvement of locomotion in the model animals, with advantages of the human cord blood cells with respect to embryonic stem cells[35]), for the treatment of

32 Liao W., Zhong J., Yu J., Xie J., Liu Y., Du L., Yang S., Liu P., Xu J., Wang J., Han Z., Han Z.C., *Therapeutic benefit of human umbilical cord derived mesenchymal stromal cells in intracerebral hemorrhage rat: implications of anti-inflammation and angiogenesis*, Cell Physiol Biochem 2009; 24 (3-4): 307-316.

33 Newman M.B., Davis C.D., Borlongan C.V., Emerich D., Sanberg P.R., *Transplantation of human umbilical cord blood in the repair of CNS diseases*, Expert opinion on Biological Therapy 2004; 4(2): 121-130. Sanberg P.R., Willing A.E., Garbuzova-Davis S., Saporta S., Liu G., Sanberg C.D., Bickford P.C., Klasko S.K., El-Badri N.S., *Umbilical cord blood-derived stem cells and brain repairs*, Annals of the New York Academy of Sciences 2005; 1049: 67-83.

34 Chen R., Ende N., *The potential for the use of mononuclear cells from human umbilical cord blood in the treatment of amyotrophic Lateral Sclerosis in SOD1 mice*, Journal of Medicine 2000; 31(1-2): 21-30. Ende N., Weinstein F., Chen R., Ende M., *Human umbilical cord blood effect on sod mice (amyotrophic lateral sclerosis)*, Life Sciences 2000; 67(1): 53-59. Garbuzova-Davis S., Willing A.E., Zigova T., Saporta S., Justen E.B., Lane J.C., Hudson J.E., Chen N., Davis C.D., Sanberg P.R., *Intravenous administration of human umbilical cord blood cells in a mouse model of amyotrophic lateral sclerosis: distribution, migration, and differentiation*, Journal of Hematotherapy and Stem Cell Research 2003; 12(3): 255-270.

35 Saporta S., Kim J.J., Willing A.E., Fu E.S., David C.D., Sanberg P.R., *Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior*, Journal of Hematotherapy and Stem Cell Research 2003; 12(3): 271-278. Zhao Z.M., Lim H.J., Liu H.Y., Lu S.H., Yang R.C., Zang Q.J., Han Z.C., *Intraspinal transplantation of CD34+ human umbilical cord blood cells after spinal cord hemisection injury improves functional recovery in adult rats*, Cell Transplantation 2004; 13(2): 113-122. Kuh S., Cho Y.E., Yoon D.H., Kim K.N., Ha Y., *Functional recovery after human umbilical cord blood cells transplantation with brain-derived neurotrophic factor into the spinal cord injured rat*, Acta Neurochirurgica (Wien) 2005; 147(9): 985-992. Lim J.H., Byeon Y.E., Ryu H.H., Jeong Y.H., Lee Y.W., Kim W.H., Kang K.S., Kweong O.K., *Transplantation of canine umbilical cord blood-derived mesenchymal cells in experimentally induced spinal cord injured dogs*, Journal of Veterinary Science 2007; 8(3): 275-282. Lee J.H., Chang H.S., Kang E.H., Chung D.J., Choi C.B., Lee J.H., Hwang S.H., Han H., Kim H.Y., *Percutaneous transplantation of human umbilical cord blood-derived multipotent stem cells in a canine model of spinal cord injury*, Journal of Neurosurgery 2009; 11(6): 749-757.

ischemic lesions of the limbs (the endothelial progenitor cells present in cord blood induce the neo-vascularisation of the affected limb[36]), for the treatment of myocardial infarct (the mononucleate progenitor cells present in the cord blood induce a reduction of the dimensions of the infarcted region and an improvement in the ventricular function; they intervene mostly in the process of neo-angiogenesis, thereby acting against the formation of scars and preventing ventricular dilation[37]). Furthermore, an improvement of the clinical condition has been observed in babies with Krabbe's disease[38], in babies struck by cerebral

36 Murohara T., *Therapeutic vasculogenesis using human cord blood-derived endothelial progenitors*, Trends in cardiovascular Medicine 2001; 11(8): 303-307. Uzan G., Vanneaux V., Delamu C., Ayoubi F., Gluckman E., Larghero J., *Les progéniteurs endothéliaux circulant du sang de cordon: perspectives thérapeutiques pour les maladies cardovasculaires*, Bulletin de l'Académie Nationale de Médecine 2009; 193(3): 537-541. Vanneaux V., El-Ayoubi F., Delmau C., Driancourt C., Lecourt S., Grelier A., Cras A., Cuccuini W., Soulier J., Lataillade J.J., Lebousse-Kerdlles M.C., Outry J.F., Sibony O., Marolleau J.P., Benbunan M., Uzan G., Larghero J., *In vitro and in vivo analysis of endothelial progenitor cells from cryopreserved umbilical cord blood: are we ready for clinical application ?*, Cell Transplantation 2010, epub ahead of print.

37 Henning R.J., Abu-ali H., Balis J.U., Morgan M.B., Willing A.E., Sanberg P.R., *Human umbilical cord blood mononuclear cells for the treatment of acute myocardial infarction*, Cell Transplantation 2004; 13(7-8): 729-739. Hirata Y., Sata M., Motomura N., Takanashi M., Suematsu Y., Ono M., Takamoto S., *Human umbilical cord blood cells improve cardiac function after myocardial infarction*, Biochemical and Biophysical Research Communications 2005; 327(2): 609-614. Ma N., Stamm C., Kaminski A., Li W., Kleine H.D., Muller-Hilke B., Zhang L., Ladilov Y., Egger D., Steinhoff G., *Human cord blood cells induce angiogenesis following myocardial infarction in NOD/scid-mice*, Cardiovascular Research 2005 ; 66(1) : 45-54. Hu C.H., Li Z.M., Du Z.M., Zhang A.X., Yang D.Y., Wu GF, *Human umbilical cord-derived endothelial progenitor cells promote growth cytokines-mediated neovascularisation in rat myocardial infarction*, Chinese Medical Journal 2009; 122(5) : 548-555. Ghodsizad A., Nehaus M., Kögler G., Martin U., Wernet P., Bara C., Khaladj N., Loos A., Makoui M., Thiele J., Mengel M., Karck M., Klein H.M., Haverich A., Ruhpanwar A., *Transplanted human cord blood-derived unrestricted somatic stem cells improve left-ventricular function and prevent left-ventricular dilation and scar formation after acute myocardial infarction*, Heart 2009; 95(1) : 27-35. Wu K.H., Zhou B., Yu C.T., Cui B., Lu S.H., Han Z.C., Liu Y.L., *Therapeutic potential of human umbilical cord derived stem cells in a rat myocardial infarction model*, Annals of Thoracic Surgery 2007; 83(4): 1491-1498.

38 Escolar M.L., Poe M.D., Provenzale J.M., Richards K.C., Allison J., Wood S., Wenger D.A., Pietryga D., Wall D., Champagne M., Morse R., Krivit W., Kurtzberg J., *Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease*, The New England Journal of Medicine 2005; 352(20): 2069-2081.

palsy,[39] in one adult patient with a lesion of the spinal marrow[40] and in patients with Buerger's disease.[41] There appear to be promising, although not conclusive, results from a clinical study with autologous umbilical cord blood infusions in patients with diabetes type 1.[42]

Finally, we must recall the fact that at present around 90% of the units of cord blood donated is unsuitable for preservation for use for transplant purposes. Blood not suitable for transplant, however, could be used either for purposes of research or for the production of blood components and in particular for platelet gel.[43] "Platelet gel is a blood component for cutaneous use, of autologous or of allogeneic origin, obtained from the aggregation of a platelet concentrate brought into contact with calcium and with biological factors or pharmacological factors favourable to aggregation (...). Cutaneous use of the preparation, favoured by its characteristics of plasticity and of being susceptible to modelling at the site of application, fosters and accelerates tissue repair, whether cutaneous or of the bones. Its greatest use is to be found in maxilla-facial surgery, orthopaedic surgery and in the treatment of torpid cutaneous ulcers. The preparation can be obtained from whole blood from a 'pre-donation' on the part of the person concerned or from allogeneic donation by a process of splitting, with or without re-infusion of the red globules or of either autologous or allogeneic platelet-rich plasma. The whole process must take place with the guarantee of asepsis. Once the preparation has been obtained, it must be used as soon as possible or otherwise it must be frozen, in accordance with the criteria pertaining to time and to modalities employed for fresh congealed plasma (PFC). In the case of allogeneic origin, the tests required for biological validation must be followed".[44] The possibilities of using platelet gel have been expanded progressively to various areas of medicine (including surgical) on account of its reparative capacities.[45] The option of not losing cord blood, when this proves to be unsuitable for preservation for transplant purposes, offers a genuine opportunity to highlight the fact that the donation is an act of solidarity.

39 Reimann V., Creutzig U., Kögler G., *Stem cells derived from cord blood in transplantation and regenerative medicine*, Deusches Ärtzteblatt International 2009; 106(50): 831-836. Papadopoulos K.I., Chanthachorn S., Paisan M., Unkarunwong A., *Safety and feasibility of Autologous Umbilical Cord Blood Stem Cell Intravenous Infusion in a toddler with Spastic Diplegia/Cerebral Palsy: a Case Report*, Thai Stem Life Bangkok, Thailand, 23rd Royal Thai COG Abstract, 2008. Papadopoulos K., Low S., Aw T.C., *Safety and Feasibility of autologous umbilical cord blood stem cell intravenous infusion in toddlers with cerebral palsy and the role of low-dose G-CSF IM injections*, 2nd International Congress on Responsible Stem Cell Research, Nov. 26-28 Monaco, Abstract n°24. *Toddler Sees Dramatic improvement From Stem Cell Treatment As Documented by US Hospital Medical Report*, Medical News Today,16 August 2007.

40 Kang K.S., Kim S.W., Oh Y.H., Yu J.W., Kim K.Y., Park H.K., Song C.H., Han H., *A 37-year-old spinal cord-injured female patient, transplanted of multipotent stem cells from human UC blood, with improved sensory perception and mobility, both functionally and morphologically: a case study*, Cytotherapy 2005; 7(4): 368-373.

41 Kim S.W., Han H., Chae G.T., Lee S.H., Bo S., Yoon J.H., Lee Y.S., Lee K.S., Park H.K., Kang K.S., *Successful stem cell therapy using umbilical cord blood-derived multipotent stem cells for Buerger's disease and ischemic limb disease animal model*, Stem Cells 2006; 24(6): 1620-1626.

42 Haller M.J., Viener H.L., Wasserfall C., Berusko T., Atkinson M.A., Schatz D.A., *Autologous umbilical cord blood infusion for type 1 diabetes*, Experimental Hematology 2008; 36(6): 710-715. Haller M.J., Wasserfall C.H., McGrall K.M., Cintron M., Brusko T.M., Wingard J.R., Kellyu S.S., Shuster J.J., Atkinson M.A., Schatz DA, *Autologous umbilical cord blood transfusion in very young children with type 1 diabetes*, Diabetes Care 2009; 32(11): 2041-2048

43 Parazzi V., Lazzari L., Rebulla P., *Platelet gel from cord blood: A novel tool for tissue engineering*, Platelets 2010; 21(7): 549-54.

44 Ministero della Salute. Decreto 3 marzo 2005. Caratteristiche e modalità per la donazione di sangue e di emocomponenti. *Gazzetta Ufficiale della Repubblica Italiana* - Serie generale n. 83. 3 marzo 2005.

45 Greppi N., Mazzucco L., Galetti G., Bona F., Petrillo E., Smacchia C., Raspollini E., Cossovich P., Caprioli R., Borzini P., Rebulla P., Marconi M, *Treatment of recalcitrant ulcers with allogeneic platelet gel from pooled platelets in aged hypomobile patients*, Biologicals 2011; 39(2): 73-80.

ETHICAL ASPECTS

The growing use of cord blood in clinical practice makes it necessary for there to be an attentive ethical reflection both about its use and about the establishment of banks for the collection, preservation and distribution of cord blood. In particular it is necessary to examine four aspects:

1) Whether it is opportune to create banks for the preservation of cord blood;
2) To examin the procedures and resources used in the collection and preservation of cord blood;
3) To evaluate the advantages of public vs private cord banks;
4) To consider the ethical aspects relating to the rights of the donor woman and of her child.

I. IS IT OPPORTUNE TO CREATE BANKS FOR THE PRESERVATION OF CORD BLOOD?

This question demands that consideration be given first of all to whether, at the present time, it is necessary to create banks for the preservation of cord blood (public or private). In this regard, it must be specified that only 30% of patients who need a transplant of haematopoetic stem cells are able to find a histo-compatible relative who can donate cord blood.[46]

The evaluation of the ethics of cord blood banks requires consideration also of:

a) The potential advantages and disadvantages of the use of cord blood compared to bone marrow;
b) The ethical justification for the creation of the banks in relation to their use in a clinical setting;

46 Sullivan M.J., *Banking on cord blood stem cells*, Nature Reviews Cancer 2008; 8: 554-563.

c) The ethical justification for the creation of the cord banks in relation to their actual clinical use (as opposed to expectations of their use);

d) The ethical evaluation of the cost benefits of the preservation and use of units of preserved cord blood;

e) Limits which may arise for the preservation and use of cord blood.

a) Advantages and disadvantages of the use of cord blood, compared to bone marrow

Since at present there exist more than 19 million bone marrow voluntary donors[47], is it necessary to promote the preservation of umbilical cord blood as well? Indeed, if the use of cord blood offers advantages compared to the use of blood from the marrow, that would justify its preservation, even in the presence of a high number of specimens of bone marrow already preserved.

- *Advantages which have been established*[48] of cord blood compared to bone marrow are: a) the absence of medical risk for the newborn donor at the moment of collection; b) the absence of the risk of transmitting herpes virus c) the immediate availability of preserved units for clinical use; d) a greater possibility of having adequate specimens for ethnic minorities.

- *Potential advantages* of cord blood are: a) the number of stem cells and of progenitor haematopoetic cells sufficient to permit the transplant to take, as much in adults as in children; b) a lower risk of developing GVHD after the transplant, on the basis that the newborn is immunologically "weak"; a lower requirement of histo-compatibility between donor and recipient (which indirectly increases the possibility of finding a donor who may afford a reasonable possibility of clinical success).

47 http://www.fcarreras.org/en/spanish-bone-marrow-donors-registry_4768 (7-06-2012)

48 Wagner J.E., Gluckman E., *Umbilical cord blood transplantation: The first 20 years*, Seminars in Hematology 2010; 47: 3-12.

- *Potential disadvantages* of cord blood are: a) a greater difficulty in obtaining a stable graft, connected to the low number overall of stem cells and of progenitor haematopoetic cells contained in it; b) a higher risk of developing opportunistic infections; c) a higher risk, according to some authors, of developing a GVHD, linked to the transfer of maternal cells along with the (allogenic) transplant, involving a risk of transmitting unknown genetic diseases.

In general terms, the consideration and the balance of all these elements, demonstrating a greater advantage on the clinical level insofar as cord blood is concerned, excludes there being difficulties on the ethical plain in regard to its use.

b) The clinical use of cord blood banks

Today, the utility of the use of umbilical cord blood in patients is beyond doubt. It is used for the treatment of acute and chronic leukaemias,[49] myelodyplastic syndromes,[50] beta-thalassemia major,[51]

49 Laughlin M.J., Eapen M., Rubinstein P. et al., *Outcomes after transplantation of cord blood or bone marrow for unrelated donors in adults with leukemia*, New England Journal of Medicine 2004; 351: 2265-2267. Advani A.S., Laughlin M.J., *Umbilical cord blood transplantation for acute myeloid leukemia*, Current Opinion in Hematology 2009; 16: 124-128. Atsuta Y., Suzuki R., Nagamura-Inoue T. et al., *Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia*, Blood 2009; 113: 1631-1638.

50 Parikh S.H., Mendizabal A., Martin P.L. et al., *Unrelated donor umbilical cord blood transplantation in paediatric myelodysplastic syndrome: a single-center experience*, Biology of Blood and Marrow Transplantation 2009; 15: 948-955.

51 MacMillan M.L., Walters M.C., Gluckman E., *Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies*, Seminars in Hematology 2010; 47: 37-45. Boncimino A., Bertaina A., Locatelli F., *Cord blood transplantation in patients with hemoglobinopathies*, Transfusion and Apheresis Science 2010; 42: 277-281.

Falconi's anaemia,[52] sickle-cell anaemia,[53] severe marrow aplasia,[54] lynphoprolific syndromes,[55] severe immuno-deficiency syndromes,[56] auto-immune diseases,[57] serious metabolic dysfunctions[58] and various types of solid tumours.[59]

The broad possibility of clinical application appears to justify the use of cord blood on the ethical level, where it has a therapeutic

52 MacMillan M.L., Walters M.C., Gluckman E., *Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies*, Seminars in Hematology 2010; 47: 37-45. Gluckman E., Rocha V., Ionescu I. et al., *Results of unrelated cord blood transplant in Fanconi anemia patients: risk factor analysis for engraftment and survival*, Biology of Blood and Marrow Transplantation 2007; 13: 1073-1082.

53 MacMillan M.L., Walters M.C., Gluckman E., *Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies*, Seminars in Hematology 2010; 47: 37-45. Boncimino A., Bertaina A., Locatelli F., *Cord blood transplantation in patients with hemoglobinopathies*, Transfusion and Apheresis Science 2010; 42: 277-281.

54 MacMillan M.L., Walters M.C., Gluckman E., *Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies*, Seminars in Hematology 2010; 47: 37-45. Yoshimi A., Kojima S., Taniguchi S. et al., *Unrelated cord blood transplantation for severe aplastic anemia*, Biology of Blood and Marrow Transplantation 2008; 14: 1057-1063.

55 Gratwohl A., Baldomero H., *European survey on clinical use of cord blood for hematopoietic and non-hematopoietic indications*, Transfusion and Apheresis Science 2010; 42: 265-275.

56 Cairo M.S., Rocha V., Gluckman E. *et al., Alternative allogeneic donor sources for transplantation for childhood diseases: unrelated cord blood and haploidentical family donors*, Biology of Blood and Marrow Transplantation 2008; 14(Supplement): 44-53. Smith A.R., Gross T.G., Baker K.S., *Transplant outcomes for primary immunodeficiency disease*, Seminars in Hematology 2010; 47: 79-85.

57 Gratwohl A., Baldomero H., *European survey on clinical use of cord blood for hematopoietic and non-hematopoietic indications*, Transfusion and Apheresis Science 2010; 42: 265-275.

58 Cairo M.S., Rocha V., Gluckman E. *et al., Alternative allogeneic donor sources for transplantation for childhood diseases: unrelated cord blood and haploidentical family donors*, Biology of Blood and Marrow Transplantation 2008; 14(Supplement): 44-53. Beam D., Poe M.D., Provenzale J.M. et al., *Outcomes of unrelated cord blood transplantation for X-linked adrenoleukodystrophy*, Biology of Blood and Marrow Transplantation 2007; 13: 665-674. Escobar M.L., Poe M.D., Provenzale J.M. et al., *Transplantation of umbilical cord blood in babies with infantile Krabbe's disease*, New England Journal of Medicine 2005; 352: 2069-2081.

59 Gratwohl A., Baldomero H., *European survey on clinical use of cord blood for hematopoietic and non-hematopoietic indications*, Transfusion and Apheresis Science 2010; 42: 265-275. Cairo M.S., Rocha V., Gluckman E. *et al., Alternative allogeneic donor sources for transplantation for childhood diseases: unrelated cord blood and haploidentical family donors*, Biology of Blood and Marrow Transplantation 2008; 14(Supplement): 44-53.

purpose, and the creation of banks for the preservation of such haematopoetic material for the above-mentioned ends. In the same way, the existence of clinical studies presently under way with patients with neonatal cerebral damage,[60] and with diabetes of type 1,[61] even though these are still preliminary and further data for confirmation are awaited, support the use of cord blood.

From the ethical point of view, independently of the use of cord blood in different pathologies, it will be necessary to consider where the results obtained justify its use. In this regard, review of the literature shows that the consolidation of the transplant, when cord blood is used, is on average equal to 75-80% for children with leukaemia, 28-78% for adults with leukaemia, 70-80% in the case of non-malignant pathologies; moreover, survival is equal to 49-55% in children, 75% in adults and 80% in cases of non-malignant pathologies.[62] However, the consolidation of the transplant occurs more slowly in the case of cord blood compared to bone marrow, while the incidence of GVHD is lower in the case of the use of cord blood compared with bone marrow.[63] Furthermore, the transplant of cord blood can be effected with a lower number of HLA matching antigens, even if, ideally, 5 out 6 antigens should be combined. The units of cord blood should not contain less than 2,5x10 (power 7) nucleated cells. When these requirements are satisfied, the transplant is successfully effected in more than 50% of patients.[64]

60 Cord blood for neonatal hypoxic-ischemic encephalopathy, Duke University, Protocol clinic: NCT00593242. www.clinicaltrials.gov

61 Haller M.J., Viener H.L., Wasserfall C. at al., *Autologous umbilical cord blood infusion for type 1 diabetes*, Experimental Hematology 2008; 36(6): 710.

62 Kurtzberg J., Lyerly A.D., Sugarman J., *Untying the Gordian knot: policies, practices, and ethical issues related to banking of umbilical cord blood*, The Journal of Clinical Investigation 2005; 115: 2592-2597.

63 Rocha V., Wagner J.E., Sobocinski K.A. et al., *Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA identical sibling*, New England Journal of Medicine 2000; 342: 1846-1854.

64 Querol S., Mufti G.J., Marsh SGE et al., *Cord blood stem cells for hematopoietic stem cell transplantation in the UK: how big should the bank be?*, Haematologica 2009; 94: 536-541.

For this reason, eminent researchers such as John Wagner and Elaine Gluckman have come to the point of being able to claim that "the blood of the umbilical cord has reached the point of being one of the sources of maternal haematopoetic cells most used in allogeneic transplants.[65]

It seems, then, that the use of cord blood and the creation of banks for the collection of these biological specimens are ethically justified, at least as far as their clinical value is concerned.

c) The clinical use of banks of umbilical cords

In any event, one aspect which must be considered is whether blood and cord banks are used effectively to a sufficient degree. Under this aspect, too, it seems that the cord banks are amply justified[66], on the basis that, since the time of their first creation in New York in 1993, the number of specimens preserved in them has increased progressively as reported in the table below.

65 Wagner J.E., Gluckman E., *Umbilical cord blood transplantation: The first 20 years*, Seminars in Hematology 2010; 47: 3-12.

66 However, we should be aware that the notable variation in standards employed in procedures for the collection and preservation by the different banks makes it particularly difficult to offer an accurate economic analysis.

Year	Number of samples stored
1997	11.000
1998	22.000
1999	38.000
2000	64.000
2001	87.000
2002	128.000
2003	165.000
2004	189.000
2005	212.000
2006	252.000
2007	262.000
2008	339.000
2009	408.000
2010	450.000
2011	456.000

It is estimated that more than 20,000 units of cord blood have been used for therapeutic purposes.[67] Currently, there exist more than 100 banks of cord blood active throughout the world[68] and more than 3,500 hospitals, distributed in more than 80 countries, in which the collection of cord blood can be undertaken.[69]

As a consequence, it seems reasonable to affirm that the creation of cord blood banks is ethically justified also on the basis of the actual clinical use of units of cord blood preserved in them.

67 Gluckman E., Rocha V., *Cord blood transplantation: state of the art*, Haematologica 2009; 94: 451-454.

68 Cfr. http://www.ebmt.org/4Registry

69 Cfr. http://www.bmdw.org/index.php?id=statistics_cordblood

d) Cost-benefit advantages of the preservation and use of units of cord blood deposited in public banks

This aspect requires that there be an evaluation of whether the number of specimens of cord blood needed to satisfy the requirements of a given population can reasonably be attained; otherwise, it would be difficult to justify, on the ethical plain, the promotion of such structures. In this respect, it is estimated that 50,000 units of cord blood are sufficient for to cover the necessity of allogenic transplant for ematological diseases in a population of 60 million inhabitants, a figure attainable for most countries.[70]

Another aspect to consider is whether the economic investment necessary to obtain the number of cord blood specimens required to meet the clinical needs of society can be considered ethical. The economic data from Spain, for example, show that the minimum cost for the preservation of a unit of cord blood is equivalent to 1300 euro. The cost of maintenance is equivalent to 40 euro per year. These costs have been derived by taking into account also that 50% of the units gathered be discarded, a percentage which is an ideal, but which is difficult to attain. Therefore, if we consider that the percentage of specimens discarded could increase, it could be concluded that, if 65% of specimens were discarded, the price of preserving one unit would increase to 1600 euro, while it would increase to 1900 if 80% of specimens were discarded.[71] Thus, an approximate economic calculation, based on a rate of 50% of preserved units being discarded and on 50,000 units being preserved and on the use of 200 units per year leads to an estimate of the cost of a single unit of about 20,000 euro.[72] On the basis of these data, the minimum cost

70 Querol S., Mufti G.J., Marsh S.G.E. et al., *Cord blood stem cells for hematopoietic stem cell transplantation in the UK: how big should the bank be?*, Haematologica 2009; 94: 536-541. For example, to satisfy clinical requirements in a country such as Italy, 60,000 units of blood would suffice.

71 Querol S., Gómez S.G., Pagliuca A. et al., *Quality rather than quantity: the cord blood bank dilemma*, Bone Marrow Transplantation 2010; 45: 970-978.

72 Cfr. Plan Nacional de Sangre de Cordón Umbilical. http://www.ont.es/infesp/Paginas/PlanNacionalSCU.aspx

of preservation of 50,000 units of cord blood (the quantity necessary to meet the needs of a population of 50 million inhabitants) and with a rate of units discarded equal to 50%, it would be equivalent to circa 65 million euros, a figure which could appear initially to be rather high. However, if it is considered that, in a country like Spain, the average cost of the construction of a kilometre of highway runs at about 6 million euro, the investment necessary for the construction of 10 Km of highway would be sufficient to create a bank of 50,000 cord blood units and so to satisfy the clinical needs of the country. Obviously, to these costs would need to be added those needed to organise the hospital logistics required for the collection of the blood specimens and for their expedition to the banks.

In conclusion, it seems that the economic investment needed to create public banks of cord blood, which would collect a sufficient number of specimens to satisfy the clinical needs of whatever country, can be said to be ethically justified[73].

e) Limits on preservation for the use of cord blood

One technical aspect, but one which is of undoubted ethical relevance, concerns the period of time over which the specimens of cord blood may be preserved in good condition, such as to make possible their eventual clinical use. In fact, if such specimens were to run into the problem of early deterioration, then probably their preservation also would turn out not to be ethically justified, by reason of the fact that many of them would end up in the position of not being adequate for use at the time in which a clinical need would present itself. In this sense it has been demonstrated that specimens of blood,

73 However, it should be kept in mind that the largest amount of blood preserved from allogeneic donations stems from populations of Caucasian race and of European descent. The presence of migrant ethnic minorities in different countries makes it difficult, if not impossible, to ensure a complete cover for potential requests, which may come from those populations already now mixed. For example, in the case where an individual of European-Caucasian extraction marries an individual of African descent, a new combination of the HLA system would be created, which it would be difficult to cover from the public cord banks.

when preserved in banks which are appropriately equipped, can be maintained in suitable conditions for at least 15 years.[74] However, according to HE Broxmeywer, specimens of cord blood could be preserved in good conditions for up to 23 years.[75]

On the basis of data reported so far, therefore, it can be affirmed that, from an ethical point of view, the creation of banks of cord blood is justified in relation to the factors which are relevant to their creation and maintenance.

74 Broxmeyer H.E., Srour E.F., Hangoc G. et al., *High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years*, PNAS 2003; 100: 645-650.

75 Broxmeyer H.E., *Umbilical cord transplantation: Epilogue*, Seminars in Hematology 2010; 47: 97-103.

II. THE PRESERVATION AND STORAGE OF UMBILICAL CORD STEM CELLS

Ethical aspects relating to the preservation and storage of cord blood are linked not so much to the nature of the cord cells as to technical questions pertaining to the collection and preservation of these cells, aspects which need to be considered in the light of the principle of the proportionality of medical treatments. In the present state of our knowledge, the procedures for the collection, preservation and storage of cord blood cells do not give rise to particular difficulties and the expectation that, in future, these sources of stem cells may play an increasingly significant role in the treatment of diseases, especially of those of a degenerative nature, is more than reasonable. Therefore, the fundamental question is whether the present engagement of resources for the collection and the preservation of cord blood is proportionate to the foreseen benefits, at present and / or in the future. An adequate evaluation of the proportionality of using such resources requires that first of all that we possess an adequate knowledge of the procedures involved and of their costs; to be evaluated in terms of the use of resources, both economic and human.

It has been seen that it is possible to preserve the cells of umbilical cord blood through freezing at – 196°C; after thawing it is also possible to transfer such cells into a host organism without their losing their property of being able to repopulate. Such circumstances allow the long term storage of umbilical cord blood in so-called "cord blood banks". The prospect of this has attracted public attention, especially in relation to the increasing diffusion of information about the multiple properties of stem cells derived from the umbilical cord. Such interest could be destined to increase further after the announcement of the possibility of deriving induced pluripotent stem cells (IPSs, *induced pluripotent stem cells*) from cord stem cells.

The banks for preserving cord blood are true and proper "banks", where the units of cord blood are stored. After being collected in

the delivery room, the unit of cord blood is sent to the bank, where it is subjected to a series of specific tests to verify its suitability for preservation and to define its immunological characteristics, for the purpose of the analysis of compatibility between donor and recipient.

a) History of the establishment of Umbilical Cord Blood banks

The first bank for the preservation of cord blood was created in New York city in 1991, through the initiative of P. Rubinstein, soon after the first successful transplant of umbilical cord blood by E. Gluckman in 1989.[76] In 1993 the first two transplants of cord blood coming from donors without links of kinship with the recipient were effected, using these banks, while in 1996 the results were published of the first important series of these transplants.[77] These result have demonstrated that, to facilitate transplants of umbilical cord blood, it might be advisable to have available throughout the world large quantities of cord blood units, with good characteristics and of high quality. From that time onwards many researchers began to develop protocols for the collection, storage and release of cord blood units for transplants to potential recipients, who might or might not have links of kinship to the donors of these blood units. The affirmation, from 1992 onwards, that GVHD (graft versus host disease) was less serious and less frequent in transplants of umbilical cord blood, compared with transplants with haematopoetic stem cells from bone marrow, has stimulated both the clinical use of cord blood and, as a consequence, the need to establish public banks of cord blood, following the

76 Rubinstein P., Rosenfield R.E., Adamson J.W., Stevens C.E., *Stored placental blood for bone marrow reconstitution*, Blood 1993; 81(7): 1679-1690. Rubinstein P., Taylor P.E., Scaradavou A., Adamson J.W., Migliaccio G., Emanuel D., Berkowitz R.L., Alvarez E., Stevens C.E., *Unrelated Placental Blood for Bone Marrow Reconstitution: Organisation of the Placental Blood Program*, Blood Cells 1994; 20(2-3): 587-600.

77 Kurtzberg J., Laughlin M., Graham M.L., Smith C., Olson J.F., Halperin E.C., Ciocci G., Carrier C., Stevens C.E., Rubinstein P., *Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients*, The New England Journal of Medicine 1996; 335(3): 157-166.

model of the bank established by P. Rubinstein. Between 1992 and 1993 different public banks opened up also in Europe (Paris, Milan, Düsseldorf, Liège and the United Kingdom). The possibility, reported in 1994, of conducting a successful transplant of umbilical cord blood from a donor extraneous to the recipient and with only partial HLA compatibility has further stimulated the creation of such banks.

The multiplication of cord blood banks throughout the world has led to the establishment of different networks between banks, both at the national and international level, to foster the exchange of information between the various centres. The largest international register regarding bone marrow and cord blood is the *Bone Marrow Donors Worldwide* (BMDW), which started in 1998, and has its offices in Leiden (Holland) . It results from a voluntary collaboration between the registers of donors of bone marrow and the registers from banks of cord blood. Its scope is to furnish centralised and anonymous information relating to HLA phenotypes and other pertinent data relative to bone marrow donors and to units of cord blood. At present the BMDW constitutes the largest database in the world, including 14 million donors of stem cells and cord blood units and gathering together the data of 44 cord blood banks in 26 countries. In 1994 the *European cord blood banking group* was established to manage the collection of cord blood at a European level, to standardise procedures for collection and for preservation of blood units, to set up ethical guidelines for the use of these units, and to facilitate international cooperation in this sector, through different institutions.[78] Subsequently, there have emerged numerous other international networks, for a description of which people should refer to the relevant paragraph in the section 'Normative Aspects' of the present document.

78 Gluckman E., *European Organization for Cord Blood Banking*, Blood Cells 1994; 20(2/3): 601-608.

b) Types of cord blood banks

There are three types of cord blood bank, according to the type of donation and use of the cords:

1) Unrelated, allogeneic cord blood banks, between persons who are HLA identical or not identical. Banks of allogeneic umbilical cord blood, not related by kinship, are in general public banks, established by public centres for transplants. The principle which regulates the contribution of units of cord blood in these banks is that of the altruistic gift of cord blood, comparable to the donation of blood to the transfusion services or to the donation of organs in the context of transplants. The donation is anonymous, but it should be indicated on the health card of the child and it should be possible to trace the donor. He could thus, et least theoretically, have access to his own placentary blood, if, at a specific point in his life, he needed a boost of haematopoietic stem cells. The cords stocked in these banks are enlisted in a national and in an international register, along with a note of their characteristics (concentration in cells) and their HLA type. The collection, treatment, preservation of the cords and their export follow criteria fixed at the international level,[79] which guarantees the quality of the units and their reliability. The quality of the units to be preserved has priority over their quantity.[80] The majority of public cord blood banks in the world are accredited or are in the process of gaining accreditation with NETCORD and follow the *Netcord-FACT* standards.[81]

79 Brunstein C.G., Wagner J.R., *Umbilical cord blood transplantation and banking*, Annual Review of Medicine, 2006; 57: 403-417. Navarette C., Contreras M., *Cord blood banking: a historical perspective*, British Journal of Haematology 2009; 147(2): 236-245.

80 Querol S., Gomez S.G., Pagliuca A., Torrabadella M., Madrigal J.A., *Quality rather than quantity: the cord blood bank dilemma*, Bone Marrow Transplant 2010 (Epub ahead of print).

81 *NetCord-FACT International Standards for Cod Blood Collection, Banking, and Release for Administration*, Fourth edition, January, 2010.

2) Related family cord blood banks (by kinship)[82], within the family setting, between brothers and sisters HLA identical. The collection of cord blood from relatives, in a family, can be a 'directed deposit', where the cord blood is collected from a brother of the patient at his birth, with a view to treating this patient. The problem encountered with this type of collection is that, too often, (70% of cases) the cord blood collected does not have a perfect HLA correspondence with the relative who is a recipient candidate and that it is improbable that these units will be used one day in the future for the patient for whom they were destined.
3) Autologous cord blood banks. Banks of autologous cord blood are, in general, private banks, with the aim of making a profit, which, on the basis of a payment, preserve blood from the umbilical cords of children born in a specific family with a view to the eventual use of this blood within the family (among relatives) or for the child himself (autologous).

Finally, there is the possibility of mixed cord blood banks that perform a 'combined donation'.

82 Cfr. Comité Consultatif National d'Éthique pour les Sciences de la Vie et de la Santé, *Utilisation des cellules souches issues du sang de cordon ombilical, du cordon lui-même et du placenta et leur conservation en biobanques, Questionnement éthiqu*, (AVIS n° 117, 23-II-2012).

III. PUBLIC *vs* PRIVATE BANKS: HOW TO MAXIMISE THE BENEFITS FOR THE INDIVIDUAL AND FOR SOCIETY

One ethical question which is the object of particular discussion concerns which typology of bank should be promoted, whether the public bank or the private bank.[83] It is a matter where debate is needed because, at its base, are personal and social attitudes which stand in opposition to one another. The first ethical controversy in this regard surrounds the question of whether it is appropriate or not to promote the creation of banks for the preservation of autologous cord blood. In this regard, it is necessary to consider, first of all, what probabilities there are that units of cord blood may be used, in the relatively near future, for the child who has donated the cord. Early scientific data on this issue indicate a probability of use between 1/2,700 and 1/20,000[84]. The figures for the probability of needing an allogeneic hematopoietic stem cell transplantation are 0.04% by age 20, 0,10% by age 40 and 0.25% by age 70 years[85], higher than generally appreciated. But this cannot be directly translated into the likelihood of using a stored cord blood unit for autologous transplantation. From a recent study which involved 57 specialist centres in the United States and Canada, which habitually undertake blood marrow transplants, it emerges that only on 9 occasions was autologous cord blood used.[86] Similarly,

83 Fisk N.M., Roberts I.A.G., Markwald R. et al., *Can routine commercial cord blood banking be scientifically and ethically justified*, PLoS Medicine 2005; 2: 87-90. Ecker J.L., Greene M.F., *The case against private umbilical cord blood banking*, Obstetrics and Gynecology 2005; 105: 1282-1284. Sugarman J., Kaalund M., Kodish E. et al., *Ethical issues in umbilical cord blood banking. Working group on ethical issues in umbilical cord blood banking*, JAMA 1997; 278: 938-943.

84 Johnson F.L., *Placental Blood Transplantation and Autologous Banking-Caveat Emptor*, Journal of Pediatric Hematology/Oncology 1997; 19(3): 183-186.

85 Nietfeld J.J., Pasquini M.C., Logan B.R .et al., *On the probability of using cord blood*, Biology of Blood and Marrow Transplantation 2008; 14: 724-725. Nietfeld J.J., Pasquini M.C., Logan B.R. et al., *Lifetime probabilities of hematopoietic stem cell transplantation in the U.S.*, Biology of Blood and Marrow Transplantation 2008; 14: 316-322.

86 Thornley I., Eapen M., Sung L. et al., *Private cord blood banking: experiences and views of pediatric hematopoietic cell transplantation physicians*, Pediatrics 2009; 123: 1011-1017.

the data released by the Italian Ministry of Health report only three cases of the autologous use of cord blood.[87] Of all these, however, only one was proven and concerned a girl of four years of age affected by acute leukaemia.[88] Certainly, there could be some other cases of the autologous use of cord blood in existence, not published in the literature; nevertheless, it seems that it can be affirmed, with a fair degree of certainty, that such use at present is a rather rare occurrence.[89] On the basis of these data, therefore, it is difficult to conclude that there is an ethical justification for the preservation of autologous cord blood, at least in regard to the probability of its effective clinical use.[90]

Another ethical dimension concerns the cost of autologous transplantation, taking into account the number of units presently preserved and the transplants undertaken. At the present time about 1.3-1.4 millions of units of cord blood are preserved in private banks throughout the world. Insofar as there is only one example of an autologous transplant confirmed in haematological malignancy[91] and only another three are very probable and since a unit of cord blood preserved in a bank which is well equipped for 20 years represents a cost which hovers around 1500-2500 euros for depositing the blood specimen and about 150 euro per year for its preservation (thus a further 3000 euro altogether), the result is that the preservation of these 80,000 units of blood for a period equivalent to 20 years would

87 Ferreira E., Pasternak J., Bacal N. et al., *Autologous cord blood transplantation*, Bone Marrow Transplantation 1999; 24: 1041. Fruchtman S.M., Hurlet A., Dracker R. et al., *The successful treatment of severe aplastic anemia with autologous cord blood transplantation*, Biology of Blood and Marrow Transplantation 2010; 10: 741. Hayani A., Lampeter E., Viswanatha D. et al., *First report of autologous cord blood transplantation in the treatment of a child with leukemia*, Pediatrics 2007; 119: 296.

88 Viswanatha D. et al., *First report of autologous cord blood transplantation in the treatment of a child with leukemia*, Pediatrics 2007; 119: 296.

89 Samuel G.N., Kerridge I.H., O'Brien T.A., *Umbilical cord blood banking: public good or private benefit?*, The Medical Journal of Australia 2008; 188: 533-535.

90 With the exception of subjects of mixed race (for example Caucasian-African), as already indicated in paragraph 73.

91 Notwithstanding the fact that clinical trials exist also for other clinical situations (eg. in children with diabetes mellitus or with cerebral palsy), use at the moment remains low.

cost 2,400 million euros. Hence there is a duty to ask whether such an economic expenditure for the treatment of only one patient and, in any case, certainly less than a hundred, would be ethical. Notwithstanding these considerations, it could be said that the economic investment required for the autologous preservation of cord blood in private banks could be freely sustained by the parents of the child who gives the cord, who certainly have the right to direct their money to ends which they judge most appropriate – according to the principle of the free use of private property – and especially in view of the possibility, however remote it may be, of offering the opportunity of treatment to the child, in the event that the need presented itself. However, if it is considered that private money also has a social function, then it would be necessary to ask whether these 2,400 million euros, even if they come from private individuals, could be spent for purposes of greater social relevance, even within the context of health care itself.

Apart from the limited possibility of clinical application and a sparse economic return, the autologous use of cord blood presents some other medical contra-indications, linked to the presence of chromosomal trans-locations in blood cells of babies who subsequently have developed leukaemia.[92] For this reason the American Academy of Pediatrics considers as potentially contra-indicated the autologous transplant of cord blood in babies with lymphoproliferative diseases.[93] Still on the basis of this difficulty, the creation of banks of cord blood for autologous use has been prohibited in some countries;[94] to overcome

92 Zipursky A., *Fetal origin of leukemia and autologous cord blood transfusions*, Pediatric Research 2000; 47: 574. Rowley J.D., *Backtracking leukemia to birth*, Nature Medicine 1998; 4: 150-151. Greaves M.F., Wiemels J., *Origins of chromosome translocations in childhood leukaemia*, Nature Reviews Cancer 2003; 3: 639-649.

93 Rowley J.D., *Backtracking leukemia to birth*, Nature Medicine 1998; 4: 150-151. Leonard M.B., *Glucocorticoid-induced osteoporosis in children: Impact of the underlying disease*, Pediatrics 2007; 119(Supplement 2): 166-174. American Academy of Pediatrics Section on Hematology Oncology, American Academy of Pediatrics Section on allergy Immunology, Lubin B.H., Shearer W.T., *Cord blood banking for potential future transplantation*, Pediatrics 2007; 119: 165-170.

94 Thornley I., Eapen M., Sung L. et al., *Private cord blood banking: experiences and views of pediatric hematopoietic cell transplantation physicians*, Pediatrics 2009; 123(3): 1011-1017.

this legal impediment, some parents choose to preserve the units of cord blood in countries in which the creation of such banks, on the contrary, is authorised.

Although the cord blood preserved for autologous purposes may have a low probability of being used clinically, there would be other possible applications which could justify the creation of private banks for its preservation, as, for example, its use in the context of regenerative medicine, on the basis that the capacity on the part of cells of cord blood for trans-differentiation in nerve cells, in heart, hepatic, pancreatic, bone and cartilage cells has been demonstrated.[95] From this perspective, then, the cord blood could be used for the repair of a damaged organ in the patient himself or in one of his relatives.[96] However, this is a question of a possibility yet to be confirmed, even if numerous clinical studies currently in progress on adult stem cells (3417) and with the blood of the umbilical cord (about 196)[97] give reason to think that this possibility may become a concrete reality, at least in the medium or long term. Furthermore, the presence of mesenchymal type cells in the umbilical cord[98] – from which it has been possible to derive cells of different tissues such as bone tissue, fat tissue, cartilage tissue[99] – would expand further autologous use (in the patient or among his relatives) in the

95 Porada G.A., Porada C., Zanjani E.D., *The fetal sheep: a unique model system for assessing the full differentiative potential of human stem cells*, Yonsei Medical Journal 2004; 45(suppl): 7-14. Kogler G., *A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential*, The Journal of Experimental Medicine 2004; 200: 123-135.

96 Kurtzberg J., Lyerly A.D., Sugarman J., *Untying the Gordian knot: policies, practices, and ethical issues related to banking of umbilical cord blood*, The Journal of Clinical Investigation 2005; 115: 2592-2597. Thornley I., Eapen M., Sung L. et al., *Private cord blood banking: experiences and views of pediatric hematopoietic cell transplantation physicians*, Pediatrics 2009; 123(3): 1011-1017. Cord blood Registry (online), http://www.cordblood.com/ (2007). Ballen K.K., Barker J.N., Stewart S.K. et al., *Collection and preservation of cord blood for personal use*, Biology of Blood and Marrow Transplantation 2008; 14: 356-363.

97 Clinical trials. http://clinicaltrials.gov (accesso 6-07-11).

98 Bieback K, Klüter H., *Mesenchymal stromal cells from umbilical cord blood,* Current Stem Cell Research and Therapy 2007; 2: 310-323.

99 Bianco P., Robey P.G., Simmons P.J., *Mesenchymal Stem Cells: Revisiting History, Concepts, and Assays*, Cell Stem Cell 2008; 2: 313-319.

context of regenerative medicine.[100] The umbilical cord also contains progenitor endothelial cells,[101] which can be used to repair damaged blood vessels; in any event, it is foreseen that a large time span will still be needed before this hypothesis becomes a clinical application.

Finally, there would seem to be a further possibility of the use of the umbilical cord relative to the production of iPS cells;[102] in this case too, however, a series of technical difficulties needs to be overcome before reaching the stage of clinical application.[103]

Another reason which urges against the institution of private banks is that such banks would go against the principle of social solidarity, in that the blood units would be reserved for the exclusive use of the person of the donor and of his relatives.[104] The debate is situated, therefore, between the principle of social solidarity and the rights of individual liberty.. Those who support the creation of public banks for the preservation of cord blood claim that any free, individual decision should, nevertheless, respect the principle of social justice. On the other hand, those who support the creation of private banks claim that it is not right to invoke the controversy between individual liberty and social solidarity because not all free actions have to be ordered to social solidarity – although the latter could be desirable – insofar as solidarity must be exercised freely. In this specific case, in

100 Uccelli A., Moretta L., Pistoia V., *Mesenchymal stem cells in health and disease*, Nature Reviews Immunology 2008; 8: 726-736.

101 Au P., Daheron L.M., Duda D.G. et al., *Differential in vivo potential of endothelial progenitor cells from human umbilical cord blood and adult peripheral blood to form functional long-lasting vessels*, Blood 2008; 111: 1302-1305. Prockop D.J., *Repair of tissues by adult stem/progenitor cells (MSCs): controversies, myths, and changing paradigms,* Molecular Therapy 2009; 17: 939-946.

102 Haase A., Olmer R., Schwanke K. et al., *Generation of induced pluripotent stem cells from human cord blood,* Cell Stem Cell 2009; 5: 434-441. Giorgetti A., Montserrat N., Aasen T. et al., *Generation of induced pluripotent stem cells from human cord blood using OCT4 and SOX2*, Cell Stem Cell 2009; 5: 353-357.

103 Saha K., Jaenisch R., *Technical challenges in using human induced pluripotent stem cells to model disease*, Cell Stem Cell 2009; 5: 484-595.

104 ACOG Committee Opinion Number 399, *Umbilical cord blood banking*, Obstetrics and Gynecology 2008; 111: 475-477.

fact, freedom is considered a priority value with respect to solidarity. However much such a claim may be reasonable, it will be necessary, even so, in some cases to consider that the lack of solidarity will empty individual actions, freely undertaken, of their value. Moreover, public banks, insofar as they are financed by the State, have the possibility of being able to respond to the health needs of all citizens, thereby giving effect to the right to health of all persons, which constitutes one of the fundamental human rights.

Another ethical aspect, linked to the principle of social justice, concerns the fact that some women who wish to donate the umbilical cord, find themselves in the situation of not being able to do so in practice because, in their country or in their region, the legal or technical presuppositions for effecting the collection and preservation of cord blood do not exist.

A further ethical problem could arise from the fact that, for reasons of economy or of profit, units of blood preserved in private banks, may not be subjected to the same controls required for preservation in public banks, which could lead to an inferior quality of blood units stored in these private banks.[105] As has been said already for Spain, for example, between 50 and 80% of the units of cord blood received are discarded because they do not meet the technical standards required for a potential clinical use.[106] At present it seems that, in the case of private banks, there is not the same rigour of technical controls of units preserved, which thus gives rise to ethically unacceptable medical conduct.

Another source of perplexity from the ethical point of view concerns the duty on the part of preserving agencies to guarantee the preservation and the possibility of use of cord blood over a period of years, some even over fifteen years. In this case the European Ethical

105 Sun J., Allison J., Mc Laughlin C. et al., *Differences in quality between privately and publicly banked umbilical cord blood units: a pilot study of autologous cord blood infusion in children with acquired autologous disorders*, Transfusion 2010; 50: 1980-1987.

106 Plan Nacional de Sangre de Cordón Umbilical, http://www.ont.es/infesp/Paginas/PlanNacionalSCU.aspx

Group on Science and New Technologies recommends, in the case of the closure of an agency preserving units of cord blood, that the agency itself ensures the preservation and possible use of the blood units by their transfer to other banks or, if the case arises, affording the necessary compensation.[107]

Finally, from the ethical point of view, it will be necessary to check that private banks offer their clients adequate information relative to the medical and ethical aspects of the collection, preservation and storage of units of cord blood. At the moment it seems that such information is often confused or even erroneous, probably due to the economic benefits that the owners of the banks seek to obtain through them.[108] Information not appropriately provided in this case may include lists of diseases, such as pathological tumours, dysfunctions of the marrow system and genetic disease which at present require a transplant of allogeneic cord blood (of a relative or of another person), or information on diseases which could benefit from regenerative medicine, which, however, as has already been said, at the present moment constitutes only a hypothesis still awaiting clinical confirmation.[109]

An possible alternative to private cord blood banks which would be ethically acceptable is represented by "mixed" preservation banks which provide true and clear informations to their clients. This is the case with the British Virgin Health Bank.[110] The units of cord blood preserved in this bank are destined in 80% for allogeneic use and in 20% for autologous use. The limit of such a proposal lies in the fact

107 European Group on Ethics and Science and New Technologies, Ethical Aspects of umbilical cord banking. Cfr. http://ec.europa.eu/european_group_ethic/docs/avis19_en.pdf.

108 ACOG Committee Opinion Number 399, *Umbilical cord blood banking*, Obstetrics and Gynecology 2008; 111: 475-477.

109 Manegold G., Meyer-Monard S., Tischelli A. et al., *Controversies in hybrid banking: attitudes of Swiss public umbilical cord blood donors towards private and public banking*, Archives of Gynecology and Obstetrics 2010; 284: 99-104.

110 Editorial, *Umbilical cord blood banking Richard Branson's way*, The Lancet 369; 437: 2007. Mayor S., *World's first public-private cord blood bank launched in UK by Richard Branson*, British Medical Journal 2007; 334: 277.

that, at present, the 20% actually reserved for autologous use might not be sufficient, because of the low cellular content of the privately preserved units, to attain its therapeutic objective. However, there is in course a study of techniques of cellular expansion,[111] for the purpose of increasing the cellularity of the specimens preserved and thereby of rendering them suitable for clinical use. At present 50% of the entries into Virgin Bank are destined precisely for this type of research.[112]

A further alternative, applied for example by Spain, consists in the possibility of preserving specimens of cord blood for autologous use in public banks, on the condition, however, of being able to donate such specimens, if in time it should prove necessary for some patient not related to the family of the donor. This possibility, however, could render void the priority objective for which the cord blood is preserved, that is its use on the part of the subject who has donated it or on the part of one of his relatives.

The position of some scentific organisms and of public institutions in relation to cord blood banks

In general, it can be said that, for reasons elaborated above, groups of experts and public authorities are not in favour of the establishment of private banks for the preservation of cord blood.[113] Serious ethical reservations have been expressed along these lines by

111 Jaroscak J., Goltry K., Smith A. et al., *Augmentation of umbilical cord blood (UCB) transplantation with ex vivo-expanded UCB cells: results of a phase 1 trial using the Astrom Replicell System*, Blood 2003; 101: 5061-5067. Delaney C., Heimfeld S., Brashem-Stein C. et al., *Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution*, Nature Medicine 2010; 16: 232–236.

112 Mayor S., *World's first public-private cord blood bank launched in UK by Richard Branson*, British Medical Journal 2007; 334: 277.

113 Wagner J.E., Gluckman E., *Umbilical cord blood transplantation: The first 20 years*, Seminars in Hematology 2010; 47: 3-12. Ministero del Lavoro, della Salute e delle Politiche Sociali, *Uso appropriato delle cellule staminali del sangue del cordone ombelicale. Elementi informativi essenziali*, 14-05-2009. Katz G., Mills A., *Cord blood banking in France: Reorganizing the national network*, Transfusion and Apheresis Science 2010; 42: 307-316.

the *European Group of Ethics and Science and New Technologies*.[114] The *Convention of Oviedo* itself would seem to indicate a position contrary to the autologous preservation of cord blood where, in art. 21, it recommends that "The human body and its parts shall not, as such, give rise to financial gain.".[115] In the same way, the World Association of Bone Marrow Donors, calls into question the creation of cord banks for autologous use on the basis that, at the moment, such banks do not have any real clinical application, but "promise more than they can offer".[116] The following bodies have also expressed themselves in an analogous way: the *Royal College of Obstetricians and Gynaecologists of the United Kingdom*,[117] the *Royal British College of Obstetricians*,[118] the *Belgian consultative committee on bioethical questions*,[119] the *Swiss society of gynaecology and obstetrics*,[120] *the French academy of medicin*e,[121] *the*

114 European Group on Ethics in Science and New Technologies to the European Commission. *Ethical aspects of umbilical cord blood banking*. Cfr. http://ec.europa.eu/european_group.ethics/publications/docs/publop19_en.pdf

115 Cfr. *Convention for the protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicin*e, Oviedo 4 April 1997.

http://conventions.coe.int/Treaty/en/Treties/Html/164.htm.

116 *WMDA policy statement on the usefulness of autologous or family CBU storage*, 25 May 2006. http://www.worldmarrow.org/fileadmin/WorkingGroups_Subcommittees/Cord_Blood_Working_Group/WMDA_Policy_Statement_Final_02062006.pdf

117 Royal College of Obstetricians and Gynaecologists. *Scientific advisory committee opinion paper 2, Umbilical cord blood banking*; June 2006. Cfr. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SAC2UmbilicalCordBanking2006.pdf

118 Royal College of Midwives, *Guidance Paper 1a: commercial umbilical cord blood collection*, RCM Midwives 2002; 5: 422-423.

119 Belgian Advisory Committee on Bioethics Opinion Nº 42 of 16 April 2007 on umbilical cord blood banks.

120 Surbek D., Seelmann K., Gratwohl A. et al., Société Suisse de Gynécologie and Obstétrique. *Don de sang de cordon: Don non dirigé, don familial (dirigé) et don à but de transplantation autologue (« Private banking »)*. Avis d'Experts Nº 10, Décembre 2002. Cfr. http://sggg.ch/files/AVIS%20%D%20EXPERTS2010.pdf.

121 Bourel M., Arcadillou R., *Rapport: Les banques de sang de cordon autologue*. Académie Nationale de Médecine.

American academy of paediatrics,[122] *the American college of Obstetricians and Gynaecologists* [123] and *the Canadian Society of Obstetrics and Gynaecology*.[124] Finally, the Italian Ministry of Health and of Social Policy, in a note regarding the appropriate use of cord stem cells, affirms that: "the indications for the preservation of cord blood at the moment of birth, for the purpose of future haematopoetic autologous transplant, do not exist at the moment", insofar as "at the present time actual scientific evidence (of utility) is in relation solely to the use of allogenic (cord) blood".[125]

122 American Academy of Pediatrics, *Cord blood banking for potential future transplantation*, Pediatrics 2007; 1: 165-170. American Academy of Pediatrics WGOCBB, *Cord blood banking for potential future transplantation: subject review. American Academy of Pediatrics. Work group on cord blood banking*, Pediatrics 1999; 104: 116-118.

123 American College of Obstetricians and Gynaecologists, *Committee opinion, umbilical cord blood banking*, Obstetrics and Gynecology 2008; 111: 475-477.

124 Armson B.A., *Maternal/fetal medicine committee, Society of Obstetricians and Gynaecologists of Canada. Umbilical cord blood banking: implications for perinatal care providers*, Journal of Obstetrics and Gynaecology Canada 2005; 27: 263-290.

125 Ministero del Lavoro, della Salute e delle Politiche Sociali, *Uso appropriato delle cellule staminali del sangue del cordone ombelicale. Elementi informativi essenziali*, 14-05-2009.

IV. SPECIFIC ASPECTS CONCERNING THE DONOR WOMAN AND HER BABY

Independently of ethical aspects linked to the promotion, development and maintenance of banks, the donation of cord blood would have to respect the ethical principles required for the normal donation of organs and tissues for the purposes of research and which are principally concerned with the informed consent to the donation, the subsequent economic benefits, the ownership of the specimens donated, the storing of information and the respect for the privacy of the donor woman and of her child.[126]

Informed consent

Obtaining informed consent involves a procedure which is indispensable for ensuring the respect for the autonomy of the donor woman. It is desirable that such consent be obtained prior to delivery, in such a way that the woman is in a setting which is suitable for her to express herself with a sufficient degree of awareness. The information contained in the consent form must include a description of the method for obtaining the specimen of cord blood in question, the transformation it will undergo and the options pertaining to the types of bank presently in existence for its storage; equally, the risk must be communicated of not being able to preserve the blood whenever the unit collected does not possess all of the quality criteria required for its preservation.

126 American Medical Association (presented by: Levine Mark A), *Umbilical cord blood banking. Report of the Council on Ethical and Judicial Affairs.* CEJA Report 9-I-07. November 2007. Cfr. www.ama_assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion2165.shtml. Petrini C., *Umbilical cord blood collection, storage and use: ethical issues*, Blood Transfusion 2010; 8: 139-148.

Respect of privacy.

Aspects relating to the storage of personal data can be said today to be sufficiently guaranteed by norms in force in various developed countries. Respect for the privacy of the donor mother and of the child requires the same precautions normally required for the collection of blood or other medical purposes. Still, it will be necessary to ensure respect for confidentiality, to an adequate degree, in any relationships which may arise between the donor mother and the bank in which the blood units are preserved.

Ownership of preserved blood.

At present, there is also discussion about the ownership of preserved blood, that is to say whether it belongs to the woman who authorised its collection and preservation or to the baby from whose cord it was obtained. Probably, the latter proposal will emerge as the most satisfactory in that, in all developed countries, the child, once born, enjoys the fulness of personal rights, from the legal point of view; hence, everything which implies the manipulation of a part of his body ought to be considered a violation of the principle of autonomy.

Conflict of interests.

Finally, it will be necessary to be suitably vigilant about possible economic interests on the part of those health-care workers who recommend the collection of cord blood, when these collaborate with private banks for the preservation of cord blood.

CONCLUDING ETHICAL CONSIDERATIONS

As we have seen so far, many criticisms have been raised about the creation of private banks for the preservation of cord blood. Nevertheless there is no ethical argument which is truly determinant against the possibility of preservation in these banks on the part of a couple who intend to avail itself of the right to exercise its autonomy and personal liberty. Moreover, such a right would be supported by the medical benefit of using one's own blood for therapeutic purposes for oneself or for a relative., a benefit further reinforced by the prospect, even though not imminent, of regenerative medicine.

These theoretical benefits notwithstanding, however, the possibilities of actual use of autologous cord blood are rather remote, a point which must not be omitted from the information given to parents at the time of collection.

In conclusion, therefore, the optimal solution would be that of creating public banks for the preservation / storage of cord blood, although sufficiently strong ethical reasons do not exists for prohibiting the creation of banks in private on the part of those who want this. It needs to be repeated, however, that public banks are more satisfactory, with respect to private banks, on the basis of the medical and ethical purposes for which they are created, and also on the basis of the principle of social justice and of social solidarity.

As far as private agencies which promote the creation of cord banks are concerned, these will need to be subjected to the normal ethical rules for commercial enterprises, that means the freedom of their commercial activity, but with respect for the truth of the information they give to their clients relative to the low probability of an actual use of autologous cord blood for therapeutic purposes.

NORMATIVE ASPECTS

I. THE NORMATIVE CONTEXT IN EUROPE

From the legislative point of view, the premise needs to be made first of all that the rapid evolution of the norms in force in this area makes it difficult to gather up-to-date documentation. Furthermore, such regulations are often interpreted in different ways according to whether the text has been brought into a juridical context, into a scientific-medical context or a medical-scientific-political context. Keeping these limits in mind, we will first present a panorama of European norms and then we will consider the legislative situation in certain European cities.

Recognising such limitations, we can identify at present three European directives - 2004/23,[127] 2006/17,[128] 2006/86[129] - which establish quality and minimal safety criteria for the donation, provision, control, working upon, preservation, storing and distribution of human tissues and cells.

In particular, with the directive 2004/23 the duty was imposed upon member States to designate one or more "competent authorities", upon whom would rest the responsibility of putting into action what the directive prescribes, in particular for what involves authorisations, accreditations and licences, as well as for what concerns organisation

127 European Parliament, Council of the European Union. Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of the European Union* 7 April 2004; L102: 48-58.

128 European Commission. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissue and cells Text with EEA relevance. *Official Journal of the European Union* 2 February 2006; L038: 40-52.

129 European Commission. Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. *Official Journal of the European Union* 25 October 2006; L294: 32-50.

and control. The directive establishes requirements, which admit of no exceptions, for the tracing, import and export checks, registration of activities, and notification of reactions and of adverse events. Implementation is then detailed in the two successive directives on the same questions. In the directive of 2006/17, in fact, specific technical prescriptions are established for each of the phases of the procedures using human tissues and cells, arranging a system of quality and safety controls, whether in cases of allogeneic preservation or in cases of autologous preservation. Under this directive, therefore, are established: requirements for the provision of human tissue and cells; criteria for the selection of donors of tissues and cells; laboratory tests required for donors; procedures for the donation and provision of tissues and/ or cells in "tissue institutes"; requirements for the direct distribution of to the recipient of specific tissues and cells. Finally, under the directive of 2006/86, the criteria are defined for granting authorisation or accreditation or licence to structures on the part of the competent authority. Under the directive it is established that, for the manipulation of blood, some fundamental requirements, envisaged in the Good Manufacturing Practices (GMP), be observed. Thus, in the directive criteria are detailed for codifying, working upon, preserving, conserving and distributing tissues and cells, the notification of adverse events and reactions, and tracking. Besides, in the case of so-called "substantial" manipulations (different from the ordinary procedures), it would be necessary to consider also the regulation of 13 November, 2007, n. 1394 on Medicinal Products for Advanced Therapies.[130] Since this is a regulation, it is directly binding upon member countries, without the need for it to be transposed into national normative structures.

It is to be observed that, in general, the directives which have been cited offer a large space to the competent authorities for the interpretation and application in different ways of what has

130 European Parliament, Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Union* 10 December 2007; L324: 121-37.

been prescribed. Such differences can be accentuated by the fact that the competent authorities designated in various nations are heterogeneous and that, depending on which country is concerned, cord blood is considered as a tissue, as a haematological product or as a pharmaceutical product.

At the present moment not all of the countries have adopted norms for banks of cord blood; in any event, in the last five years there has been a notable evolution of the organisation of bio-banks of cord blood in many European nations.

Furthermore, public banks are organised for allogeneic preservation; in general, they also allow preservation for dedicated usage for a newborn with a pathology in course at the time of birth or revealed in the pre-natal period or for dedicated usage for a blood relative with a pathology in course at the time of collection for which the use of stem cells from cord blood would be appropriate. Cord blood which, after the required analyses, is shown to be unsuitable for clinical use, could be used for purposes of research, with the permission of the mother.

At the moment there is an explicit prohibition against banks of cord blood of an autologous type in Belgium, France, Italy, Luxemburg, and not explicitly, in Dutch norms. In any case, in these countries there are bodies operating which permit export for autologous preservation abroad. In the majority of other countries one or more private banks for autologous preservation are in operation.

II. THE LEGISLATIVE SITUATION IN SOME EUROPEAN COUNTRIES

For the sake of argument we show the legislative situation in some European countries in more detail.

Austria. The directive 2004/23 was activated by the Gewebesicherheitsgesetz[131] (Tissue Safety Act) which came into force on 30 March, 2008, which also regulates the activity of cord blood banks, defines the requirements for informed consent and imposes a prohibition upon compensation or other benefits for relatives or other persons who donate cells or tissues. Moreover, a recommendation of the Supreme Council of Health[132] prohibits aggressive publicity on the part of private bio-banks and establishes certain norms for departments of obstetrics and gynaecology; it forbids every form of publicity for autologous preservation of cord blood in hospitals, imposes restrictions upon the possibilities for contacts between commercial banks of cord blood and hospital personnel, imposes a duty on a doctor in maternity wards to furnish mothers with information about the collection and preservation of cord blood.

At present in Austria there is in operation a public bio-bank at Linz hospital for the preservation of cord blood, destined for allogeneic transplants. Besides this, there are various private bio-banks in operation for autologous preservation.

Belgium. The preservation of cord blood is regulated by the law of 19 December, 2008, on the collection and preservation of tissues and other parts of the human body for therapeutic purposes and for research.[133] Article 8 of this law forbids: "1) the removal of human material or any

131 Gewebesicherheitsgesetz. *Federal Law Gazette* I 2008/49.

132 Supreme Health Council. *Resolution of the 10th Full Assembly of the Supreme Health Council on 24 May 2003*.

133 Loi relative à l'obtention et à l'utilisation de materie corporel humain destiné à des applications medicale humaines ou à des fins de recherche scientifique. *Moniteur Belge* 30 Décembre 2008:68774-87.

other operation on human material which falls within the field of the present law, which is not undertaken for a purpose which is preventative, diagnostic or for a specific and scientifically well-founded therapeutic purpose or for the purpose of a specific and pertinent piece of scientific research, whose aim has been specified; 2) every use of human bodily material in the field of the present law, which has not been undertaken for a preventative, diagnostic or specific and scientifically well-founded therapeutic purpose or for a specific and pertinent purpose of scientific research, whose aim has been specified and for which a favourable opinion has been given by an ethics committee as established by the law of 7 May, 2004, relating to experimentation upon the human person; 3) any taking of bodily material whose expected consequences for the donor are not proportionate to the purpose being pursued; 4) the removal and preservation of human bodily material destined for a deferred autologous or allogeneic use for a specific and identified recipient, unless a) at the moment of its removal and/ or obtaining it the person is suffering from or presents an exceptionally high and scientifically documented risk of a pathology for which the use of the operations just noted has been scientifically demonstrated, or b) the human bodily material remains available for therapeutic use by a third person and is registered". Hence, on the basis of such norms it emerges that preservation is only allowed for allogeneic use in terms of solidarity or for dedicated use.

At the present time in Belgium five banks for allogeneic preservation are in operation, at public university hospitals: Brussels Cord Blood Bank at Brussels, Ghent Cord Blood Bank at Ghent, Liège Cord Blood Bank at Liège, Louvain Cord Blood Bank of the Catholic University of Louvain at Louvain and Louvain Cord Blood Bank of the Catholic University of Louvain at Brussels. All the banks must obtain certification from the Ministry of Health and are affiliated to the Belgian register of bone marrow donors. No public bio-bank offers autologous preservation.

The Czech Republic, Cyprus and Croatia. In each of these countries a national bank of cord blood in operative and so are various private bio-banks for autologous preservation.

Denmark. The law of 1 April, 2006, on human tissues proclaims rules of quality and safety for bio-banks of cells and tissues. Furthermore, the law on the health service specifically envisages the existence of private bio-banks and stipulates that there must be a written contract between subjects furnishing biological specimens and the private bio-banks which preserve them. At present no public bank of cord blood has yet been established, but cooperation has been encouraged between the hospitals and the Finnish public bank of placental blood, which also serves all of the Scandinavian countries.[134] Hence, the preservation of cord blood on Danish territory turns out to be effected exclusively in three private bio-banks. As has already been said, the Finnish bank collects and distributes units of blood also for other Scandinavian countries or for Denmark, where private banks for the preservation of autologous blood are present.

Finland. The national bank of cord blood has been authorised by the nation Agency for pharmacists on 1 February, 2008.[135]

France. The Établissement Français du Sang (the French Blood Agency) and the agency of Biomedicine established in 1999 the French Network of Placental Blood. The Agency of Biomedicine is the national public structure established in 2004 with the task of coordinating the activities of donating and transplanting organs, tissues and cells, as well as the various areas of procreation, embryology and human genetics. The collection of cord blood is regulated by articles 1242-1245 of the Code on Public Health, according to which structures which preserve prepare and distribute the blood must operate according to the Good Manufacturing Practices, accepted by the French Agency of Health Safety and of Health Products. The decree of 14 September, 2009, moreover, establishes that maternity wards which undertake the collection of cord blood must be authorised by the competent health authorities.[136]

134 www.veripalvelu.fi./www/743.

135 Finnish National Agency for Medicine. License nr. 4197/4.2.5.3/2007. 1st February 2008.

136 Arrêté du 14 septembre 2009 fixant le contenu du dossier accompagnant la demande d'autorisation ou la demande de renouvellement d'autorisation d'effectuer des prélèvements de cellules à des fins thérapeutiques. Journal Officiel de la République Française 11 Octobre 2009, Annexe II. 2.

Up to now, there has not been much storage of cord blood in France; in the Réseau Français de Sang Placentaire only about 10,000 units are registered. France imports about 70% of the cord blood necessary for clinical requirements, at an ever increasing cost (2,82 million euros in 2006, 4.94 million euros in 2008).[137] Hence, efforts are being made to increase the number of maternity units in which it is possible to undertake this collection (this number should be brought within the year to 60 , equivalent to 20% of French maternity units) and to open new bio-banks (in 2009 there were three, in 2010 there were ten). The exportation of cord blood has to be authorised by the French Agency of Health Safety and of Blood Products, on the basis of an opinion of the agency for Biomedicine. The violation of the norms on the part of health professionals is punished by exclusion for up to 10 years and fines of between 30,000 (for collection) and 75,000 (for exportation) euros. The fines for structures can be up to five times heavier; their dissolution is also possible.

France imposes particularly stringent criteria of validation for collection, requiring, for example, a minimum volume of 70ml, with at least 1,8 million cells in total for preservation, whereas fifteen of the allogeneic collection banks in the United States foresee a minimum number for collection of 43 ml.[138] It can be pointed out further that, based on the law for the prevention of racial discrimination, especially restrictive in regard to the protection of personal rights, the French health authorities are encountering difficulties in gathering demographic information which would be useful for the adequate evaluation of the need for rare haplotypes. Paradoxically, the minorities, instead of being protected by that law, are subjected to an additional risk of not being able to find a suitable specimen in a French bank.

137 Inspection Générale des Affaires Sociales (Aballéa P., Vielleribière J.L.). Les conditions de l'autosuffisance en produits sanguins du marché français. 2010.

http://lesrapports.ladocumentationfrancaise.fr/cgi-bin/brp/telestats.cgi?brp_ref=114000052&brp_file=0000.pdf.

138 Committee on Establishing a National Cord Blood Stem Cell Bank Program, Meyer E.A., Hanna K., Gebbie C. (eds.). *Cord Blood. Establishing a National Cord Blood Stem Cell Bank Program* (Appendix c). The National Academy Press, Washington D.C., 2005.

In France only public banks for allogeneic collection are authorised. In some cases dedicated collection for autologous or for intra-family transplant is possible, on the basis of a list of clinical indications issued by the Agency for Biomedicine. In any case, in France, as in other countries, proposals are frequently advanced for the introduction of private banks for autologous preservation or for mixed banks[139].

The National Academy for Medicine, which had already adopted the document "Banks of autologous cord blood" on 5 December 2002,[140] published a report on 26 January, 2010, with the title: ‹‹Les cellules souches du cordon et du placenta: de la recherche aux applications thérapeutiques›› ("Cord and placenta stem cells: from research to therapeutic applications").[141]

139 For example, on 4 November, 2008 Senator Marie–Thérèse Hermange presented a report in the Senate which proposed the establishment of mixed public-private banks. Among the aims of such a proposal is the financing of banks for allogeneic collection by means of commercial banks (in part analogous to the system introduced in Spain in 2006). On 29 September, 2009, Deputy Damien Meslot deposited in the Assemblée Nationale a proposal for a law to authorise commercial banks for autologous collection, a proposal which was immediately contested by various scientific institutions. On 8 December, 2009, with obvious reference to the new proposal of law, the French Agency for Marrow Transplants and for Cellular Therapy issued a press release entitled: ‹‹Appel à la vigilance sur les sociétés privées incitant à la conservation de sang à visé autologue›› ("A call to vigilance over private societies promoting the preservation of blood for autologous use"). Two days later (10 December), the French National College of gynaecologists and Obstetricians issued a communication, in whose title the following was stated explicitly: ‹‹Non au sociétés à but lucrative incitant à la conservation de sang à visée autologue›› ("No to profit-making societies promoting blood preservation for autologous ends"), in which it was stated that autologous preservation "does not have any therapeutic interest and goes against the principles of solidarity and equality of access defended up to now by the law on Bioethics. It opens up the risk of falling into a real market system". Finally, on 21 January, 2010, the agency for Biomedicine released a communiqué under the title, itself noteworthy, of: ‹‹ Utilisation thérapeutique du sang du cordon: une clarification s'impose›› ("Therapeutic use of cord blood: a clarification is needed"), increasing from that time on also information campaigns for the public.

140 Académie Nationale de Médecine (Bourel M., Ardaillou R., eds.). *Les banques de sang de cordon autologue. Rapport au nom de la Commission 1 (Biologie – Immunologie – Génétique. Rapport adopté le 19 novembre 2002*.

www.academie-medecine.fr/upload/base/rapports_114_fichier_lie.fr.

141 Académie Nationale de Médecine (Caen J., Jouannet P., eds.). *Les cellules souches du cordone et du placenta: de la recherche aux applications thérapeutiques. Rapport adopté le 26 janvier 2010.* www.academie-medecine.fr./detailpublication.cfm?idrub=26&idligne=1772.

At last, on 7th July, 2011, after a long debate in the French Parliament, the text of law 2011-814 was adopted (published in the *Journal Officiel de la République Française*). Article 7 of this law recognises the therapeutic potential of cord blood and of haematopoetic cells, associating their status with that of tissues, cells and products of the human body. The law confirms the prohibition on preserving cord blood for personal reasons, apart from cases of proven therapeutic need recognised at the time of birth, for the newborn child or for a member of his family. Also forbidden are preservation for hypothetical future use where the need has not been scientifically proven and exportation abroad. Article 8 specifies the conditions for authorisation of structures qualified to take samples for therapeutic purposes.

Germany: The German Federal Medical Association has established "Guidelines for the transplant of stem cells of cord blood".[142] At present in Germany there exist six no-profit banks for allogeneic preservation, which offer also the possibility of dedicated preservation in the case of an indication from the family, upon the prior request of the doctor. The centres which operate transplants undertake research in the German National Registry of Blood Stem Cell Donors, ZKRD (Zentrales Knochenmarkspender Register Deutschlands).[143] Private banks are also allowed, to which the same guidelines are applied as for public banks for allogeneic preservation. However, the German Federal Medical Association recognises that, at the moment, there are no indications of which they are aware for autologous preservation.

Presently, donation is possible in about 70 places per birth for about every thousand present in the territory of the country.[144] It is estimated that only 2% of the blood from the 715,000 born in a year are preserved.

142 Bundesärztekammer (Federal Medical Association). Richtlinien zur Transplantation von Stammzellen aus Nabelschnurblut ("Guidelines for the transplantation of cord blood"). Deutsches Ärzteblatt 1999;96(19):69-76.

www.bundesaerztekammer.de/downloads/transnabel_pdf.pdf

143 www.zkrd.de.

144 www.nabelschnurblut.de.

The German private bank "Life 34" runs a site, in which all structures where it is possible to make a donation are indicated.[145]

Greece: At present regulations for banks of cord blood are lacking, since, although a law on the matter exists, the government has not appointed the "competent authority". At least 17 private banks are operating in the country.

Ireland: At the moment cord blood banks do not exist; thus, anyone needing this specific transplant generally goes to the United Kingdom (London or Newcastle).

Italy: Procedures for transfusion and the production of blood-derived products are regulated by law n. 219 of 25 October, 2005.[146] Between January, 2002, and February, 2009, there has been a succession of eight ministerial orders concerning cord blood, which have allowed preservation for allogeneic or dedicated use, and the export abroad of cord blood for autologous use, provided the procedure for prior authorisation has been followed.

145 www.vita34.de

146 Legge 21 ottobre 2005, n. 219. Nuova disciplina delle attività trasfusionali e della produzione nazionale degli emoderivati (New discipline on acts of transfusion and on the production of blood products). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 251. 27 October 2005.

On the other hand, preservation for autologous use is prohibited, as are the establishment of or publicity for banks of cord blood for private use.[147], [148], [149], [150], [151], [152], [153], [154]

147 Ministero della Salute. Ordinanza 11 gennaio 2002. Misure urgenti in materia di cellule staminali da cordone ombelicale (Ministry of Health, order 11 January, 2002. Urgent measures on the matter of stem cells from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 31. 2 June, 2002.

148 Ministero della Salute. Ordinanza 30 dicembre 2002. Misure urgenti in materia di cellule staminali da cordone ombelicale. Proroga dell'ordinanza 11 gennaio 2002. (Ministry of Health, order 30 December, 2002. Urgent measures on the matter of stem cells from the umbilical cord. Proprogation of the order of 11 January, 2002), *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 27. 2 March, 2003.

149 Ministero della Salute. Ordinanza 25 febbraio 2004. Misure urgenti in materia di cellule staminali da cordone ombelicale (Ministry of Health, order 25 February, 2004. Urgent measures on the matter of stem cells from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 65. 18 March, 2004.

150 Ministero della Salute. Ordinanza 7 aprile 2005. Misure urgenti in materia di cellule staminali da cordone ombelicale (Ministry of Health, order 7 April, 2005. Urgent measures on the matter of stem cells from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 107. 10 May, 2005.

151 Ministero della Salute. Ordinanza 13 aprile 2006. Misure urgenti in materia di cellule staminali da cordone ombelicale (Ministry of Health, order 13 April, 2006. Urgent measures onthe matter of stem cells from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 106. 5 May, 2006.

152 Ministero della Salute. Ordinanza 4 maggio 2007. Misure urgenti in materia di cellule staminali da cordone ombelicale (Ministry of Health, order 4 May, 2007. Urgent measures on the matter of stem cells from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 110. 15 May, 2007.

153 Ministero del Lavoro, della Salute e delle Politiche Sociali. Ordinanza 19 giugno 2008. Ulteriore proroga dell'ordinanza del Ministro della Salute del 4 maggio 2007, in materia di cellule staminali ematopoietiche da cordone ombelicale (Ministry of Work, Health and Social Policy, order 19 June, 2008, Further prorogation of the order of the Ministry of Health of 4 May, 2007, on the matter of haematopeotic stem cells from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 151. 30 June, 2008.

154 Ministero del Lavoro, della Salute e delle Politiche Sociali. Ordinanza 26 febbraio 2009. Disposizioni in materia di conservazione di cellule staminali da sangue del cordone ombelicale (Ministry of Work, Health and Social Policy, order 26 February, 2009, Measures on the matter of the preservation of stem cells from umbilical cord blood). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 57. 10 March, 2009.

We can mention, besides, two decrees of the Ministry of Work, Health and Social Politics of 18 November, 2009, pertaining respectively to "Measures in the matter of the preservation of stem cells from umbilical cord blood for autologous-dedicated use"[155] and the "Establishment of a national network of banks for the preservation of umbilical cord blood".[156] On the basis of the first decree, the following are permitted: preservation for allogeneic use, that is in favour of persons other than those from whom the cells are taken in the interests of solidarity, in public structures predisposed for this purpose; preservation for dedicated use for the newborn with a pathology in course at the time of birth or manifested in the pre-natal stage or for dedicated use for a blood relative with a pathology in course at the time of collection, for which the use of stem cells from cord blood would be appropriate; preservation for dedicated-autologous use in the case of specific pathologies not yet in the list attached to the decree, but for which there exist proven scientific evidence for a possible use, also in the context of clinical experimentation approved in accordance with the norms in force, provided documentation issued by a medical specialist has first been presented. In such a case the person responsible for the bank may authorise the preservation of blood from the umbilical cord, having consulted the respective multi-disciplinary technical group, coordinated by the National Transplant Centre.

However, it is possible, at one's own expense, to export the specimen of blood taken from the umbilical cord collected for autologous use, on condition of prior authorisation and counselling according to the forms established by the State / Region Agreement n. 62 of 29 April, 2010.

155 Ministero del Lavoro, della Salute e delle Politiche Sociali. Decreto 18 novembre 2009. Disposizioni in materia di conservazione di cellule staminali da sangue del cordone ombelicale (Ministry of Work, Health and Social Policy, decree 18 November, 2009, Measures on the matter of the preservation of stem cells from umbilical cord blood). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 303. 31 December, 2009.

156 Ministero del Lavoro, della Salute e delle Politiche Sociali. Decreto 18 novembre 2009. Istituzione di una rete nazionale di banche per la conservazione di sangue da cordone ombelicale (Ministry of Work, Health and Social Policy, decree 18 November, 2009, Establishment of a National network of banks for the preservation of blood from the umbilical cord). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 303. 31 December, 2009.

The Italian Cord Blood Network operates in accordance with the standards defined in national and international regulations[157] [158] (in particular standard NetCord-FACT[159]).

At present there are nineteen public banks in the country, distributed in eleven regions and operating on behalf of the National Health Service. The last one to have been established has been operative since 28 December, 2010, at Cagliari hospital. At the Galleria hospital in Genoa, on the other hand, there is the seat of the Italian Registry of Bone Marrow Donors, recognised as the Italian national register by the law of 6 March, 2001, n. 52.[160] In Italy private banks for the collection of

157 Presidente della Repubblica Italiana. Decreto legislativo 6 novembre 2007, n. 191. Attuazione della direttiva 2004/23/CE sulla definizione delle norme di qualità e di sicurezza per la donazione, l'approvvigionamento, il controllo, la lavorazione, la conservazione, lo stoccaggio e la distribuzione di tessuti e cellule umani (President of the Italian Republic, legislative decree, 6 November, 2007, n. 191. Activiation of the directive 2004/23/CE on the definition of the norms on quality and on safety for the donation, supply, control, manipulation, preservation, storage and distribution of human tissues and cells). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 261 – Supplemento ordinario n. 228/1. 9 November, 2007.

158 Presidente del Consiglio dei Ministri. Decreto legislativo 25 gennaio 2010, n. 16. Attuazione delle direttive 2006/17/CE e 2006/86/CE, che attuano la direttiva 2004/23/CE per quanto riguarda le prescrizioni tecniche per la donazione, l'approvvigionamento e il controllo di tessuti e cellule umani, nonché per quanto riguarda le prescrizioni in tema di rintracciabilità, la notifica di reazioni ed eventi avversi gravi e determinate prescrizioni tecniche per la codifica, la lavorazione, la conservazione, lo stoccaggio e la distribuzione di tessuti e cellule umani (President of the Council of Ministers, legislative decree 25 January, 2010, n. 16. Activation of the directives 2006/17/CR and 2006/86/CE, which activate directive 2004/23/CE in relation to the technical prescriptions for the donation, supply and control of human tissues and cells, as also to the prescriptions concerning traceability, notification of serious reactions and adverse events, and to the specific technical prescriptions for the codification, manipulation, preservation, storage and distribution of human tissues and cells). *Gazzetta Ufficiale della Repubblica Italiana* – Serie generale n. 40. 18 February, 2010.

159 NetCord, Foundation for the Accreditation of Cell Therapy – FACT. Cord blood accreditation manual. Fourth edition. 2010.

www.factwebsite.org/uploadedfiles/news/4th_edition_cord_blood_guidance_4.0.pdf.

160 Conferenza permanente per i rapporti tra lo Stato, le Regioni e le Province autonome di Trento e di Bolzano. Accordo atti n.62/CSR del 29 aprile 2010, ai sensi dell'articolo 35, comma 14, del decreto-legge 30 dicembre 2008, n. 207, convertito in legge, con modificazioni, dalla Legge 27 febbraio 2009, sullo schema di decreto del Ministro del lavoro, della salute e delle politiche sociali recante "Istituzione di una rete nazionale

cord blood of are prohibited; nevertheless, there are present agencies of various foreign societies (the Bioscience Institute, Cry-Save, FamiCord, Future Health, ProCrea Stem Cells, Smart Bank, and others), which export cord blood for preservation in other countries.

At present before the Chamber of Deputies and the Senate there are twelve projects for laws on the preservation of cord blood or which address the theme within the context of a broader framework.[161] The majority of these draft laws were produced in the spring of 2008, in connection with the Budget of that year, which had initially envisaged the authorisation of autologous collection, but the amendment

di banche per la conservazione di sangue cordonale". Atti n. 62/CSR del 29 aprile 2010 (Permanent conference for relations between the State, the regions and the autonomous provinces of Trent and Bolzano. Agreement acts n.62/CSR of 29 April, 2010, according to the meaning of article 35, § 14 of the legislative decree of 20 December, 2008, n. 207, converted into law, with modifications by the law of 27 February, 2009, on the scheme of the decree of the Ministry of Work, Health and Social Policy on the "Establishment of a national network of banks for the preservation of cord blood", Acta n. 62/CSR of 29 April, 2010. www.statoregioni.it/dettagliodoc.asp?idprov=8136&iddoc=26575&tipodoc=2&conf=csr.

161 Disegno di legge n. 12, primo firmatario Bianconi, depositato in Senato il 29 aprile 2008; Draft law n. 12, main signatory Bianconi, deposited in the Senate, 29 April, 2008; Disegno di legge n. 361, firmato Volontè, depositato alla Camera il 29 aprile 2008; Draft law n. 361, signatory Volonté, deposited in the Chamber of Deputies, 29 April, 2008; Disegni di legge n. 545 e 548, firmati Bertolini, depositati alla Camera il 29 aprile 2008; Draft laws n. 545 and 548, signatory Bertolini, deposited in the Chamber of Deputies, 29 April, 2008; Disegno di legge n. 340, primo firmatario Baio Dossi, depositato in Senato il 6 maggio 2008; Draft law n. 340, main signatory Baio Dossi, deposited in the Senate, 6 May, 2008; Disegno di legge n. 1214, primo firmatario Di Virgilio, depositato alla Camera il 30 maggio 2008; Draft law n. 1214, main signatory Di Virgilio, deposited in the Chamber of Deputies, 30 May, 2008; Disegno di legge n. 922, primo firmatario Cuffaro, depositato in Senato il 18 luglio 2008; Draft law n. 922, main signatory Cuffaro, deposited in the Senate, 18 July, 2008; Disegno di legge n. 1020, primo firmatario Poretti, depositato in Senato il 17 settembre 2008; Draft law n. 1020, main signatory Poretti, deposited in the Senate, 17 September, 2008; Disegno di legge n. 1267, primo firmatario De Lillo, depositato in Senato il 9 dicembre 2008; Draft law n. 1267, main signatory De Lillo, deposited in the Senate, 9 December, 2008; Disegno di legge n. 2040, primo firmatario Mosella, depositato alla Camera il 23 dicembre 2008; Draft law n. 2040, main signatory Mosella, deposited in the Chamber of Deputies, 23 December, 2008; Disegno di legge n. 2859, primo firmatario Farina Coscioni, depositato alla Camera il 27 ottobre 2009; Draft law n. 2859, main signatory Farina Coscioni, deposited in the Chamber of Deputies, 27 October, 2009; Disegno di legge n. 3691, primo firmatario Pedoto, depositato alla Camera il 4 agosto 2010; Draft law n. 3691, main signatory Pedoto, deposited in the Chamber of Deputies, 4 August, 2010.

providing for this possibility was subsequently rejected. Finally, the commitment of the Ministry of Health to ensure that there is a correct dissemination of information is to be noted.[162]

In support of the current Italian norms are to be placed also the positions expressed by the main scientific and medical associations in the country. – the Italian Society for Transfusions and Immuno-haematological Medicine (SIMTI), the Italian Bone Marrow Transplant Group (GITMO). the Italian Society for Human Genetics (SIGU), the National Federation of Obstetrics (FNCO) – which, on the occasion of the Congress on "Cord Blood: Scientific and Organisational Aspects" of 1 December, 2010 by the National Centre for Transplants (CNT) and by the National Blood Centre (CNS) at the seat of the Order of Surgeons and Dentists (OMCeO) of the province of Rome expressed their shared position as follows: "the refusal of the preservation of haematopoetic stem cells for autologous use because it is inappropriate on the scientific level; the adoption on the part of the scientific community of a single national position to show the public the value of clinical applications which have been consolidated and attention to following research projects only within protocols envisaged by current regulations; the need to set up schemes for formation at a national level dedicated to all those professionals involved in the Network, from the maternal sector to that of the child, from that of banking to that of transplants, the unsuitability of setting up new structures dedicated to the cryopreservation of units of cord blood (...), establishing eventually private banks in our country would violate the norms currently in force, contravening also the principles of voluntariness, anonymity and gratuitousness which have inspired the National health system; preservation of an autologous kind with the possibility of releasing the unit for use in terms of solidarity does not seem appropriate because in this way it would not be possible to protect the health of the possible recipient (by means of attentive clinical

162 Ministero del Lavoro, della Salute e delle Politiche Sociali. *Uso appropriato delle cellule staminali del sangue del cordone ombelicale. Elementi informativi essenziali*. 18 marzo 2009 (Ministry of Work, Health and Social Policy: Appropriate use of stem cells from the blood of the umbilical cord: Essential points of information, 18 March, 2009).

and laboratory assessments) and it would not be possible to meet the quality criteria required for the logic of transplant use (at the moment only about 30% of units collected are actually in cryon-preservation)".

The main voluntary associations have also given their adherence to this declaration: the Italian Umbilical Cord Blood Donors Association (ADISCO), the Stem Cell Donors Association (AdoCeS), the Association of Bone Marrow Donors (ADMO).

Luxemburg: There exists a law of 1 August, 2007, which explicitly forbids autologous preservation.[163]

Holland: Umbilical cord blood is treated under the law of 6 February, 2003, concerning cells and tissues, even though it is not explicitly cited. Collection and preservation take place under the responsibility of Sanquin, a non-profit organisation controlled by the Ministry of Health and with agreements with two foundations: Europdonor and EuroCord. The bank permits also dedicated preservation, when there are family indicators present.

In the country there are no private banks for autologous preservation, even if these are not expressly prohibited. In fact, autologous preservation is allowed only for dedicated use, in authorised hospital laboratories.[164] However, there are in operation bio-bank agencies from other nations for preservation abroad.

Poland: The relevant regulations are not specific, but pertain generally to organ transplants. The sole institution authorised to transfer blood is the National Transfusion Service. There are different public banks in the country for the preservation of cord blood, whose management costs remain competitive with respect to the rest of Europe.

163 Loi du 1er Août 2007 relative aux tissues et cellules humains destinés à des applications humaines (art.12), (Law of 1 August, 2007, on human tissues and cells destined for application to human beings) *Memorial Journal Officiel du Grand-Duché de Luxembourg*, 20 Août 2007, 150.

164 Federatie van Medisch Wetenscappelijke Verniginen – Dutch Federation of Biomedical Scientific Societies, Commissie Regelgevikng en Onderzoek – COREON. *Code for proper secondary use of human tissue in the Netherlands*.

www.federa.org/?s=1&m=82&p=11&v=4#868.

United Kingdom: the collection of cord blood falls back upon the responsibility of the *Human Tissue Authority*. The norms for cord blood were established by the *Human Tissue A*ct [165] (the norms on cords blood have been in force since 5 July, 2008[166]) insofar as concerns England, Wales and Northern Ireland and in the *Human Tissue Scotland Act*, very similar to the former, in regard to Scotland. in particular, the norms establish that maternity wards where collection for preservation, public or private, occurs, must guarantee the presence of personnel specifically trained for collection; ensure that procedures to effect collection are not at the expense of assistance to mother or to child; guarantee the traceability of specimens from the time of their collection until their eventual use.

There are three non-profit banks in the country for the allogeneic collection of cord blood: the National health Service cord Blood Bank (NHS CBB), the Newcastle University Hospital Bank and the Northern Ireland Cord-Blood Bank (INI CBB). Another bank is registered in Scotland, but has not yet begun collection. There are also in operation various private bio-banks for autologous preservation (one of the most well known is the Future Health Technology), which must be accredited by the Medicine and Healthcare Products Regulatory Agency (MHRA) and which must respect the requirements laid down in the Human Tissue Act.

Units of cord blood are registered at the British Bone Marrow Registry (BBMR)[167] and at Bone Marrow Donors Worldwide (BMDW) Registry,[168] for international searches. There exists, too, a registry of stem cells managed by The Anthony Nolan Trust, a non-profit organisation set up by Shirley Nolan to search for a donor compatible with her son.

165 www.legislation.gov.uk/ukpga/2004/30/contents

166 www.hta.gov.uk/media/mediareleases.cfm/418-new-rules-for-cord-blood-collection.html.

167 www.nhsbt.nhs.uk/bonemarrow/index.asp.

168 www.bmdw.org

In the United Kingdom should also be pointed out the experience of mixed public-private preservation operated by the *Virgin Health Bank*.[169] The challenge of this bank, set up by Richard Branson,[170] and which makes us of the collaboration of leaders of public opinion and scientists of worldwide renown, such as Prof. Colin McGuckin, has been that of uniting the potential of allogeneic public preservation with possible, if currently remote, applications of autologous preservation, especially in respect of some specific aspects of regenerative medicine. It is to be noted that Virgin Bank is to be distinguished from most bio-banks which often provide information which is deceptive as to possible applications, since the information that it provides to families is explicit about the fact that eventual therapeutic applications in the area of regenerative medicine are at present far from clinical practice. One peculiarity of this bank, apart from the dual system, is the fact that profit is devolved in part to research as a genuine gift. On 10 February, 2007, "The Lancet" published an editorial in which it expressed interest in the initiative from Virgin Bank.[171]

Spain. Autologous preservation has been permitted by the Royal decree 1301 of 10 November, 2006.[172] The decree envisages that all the cord blood preserved in Spain be listed in the Spanish Register of Bone Marrow Donors (Registro español de Donantes de Médula Ossea, REDMO),[173] begun in 1991 by the José Carreras International Leukaemia Foundation.[174] The National Organisation of Transplants (Organiazión Nacional de Trasplantes, ONT),

169 www.virginhealthbank.com

170 Fisk N., Atun R., *Public-private partnership in cord blood banking*, BMJ 2008; 336(7645): 642-4.

171 Editorial. *Umbilical cord blood banking Richard Branson's way*, Lancet 2007; 369(9560): 437.

172 Ministerio de Sanidad y Consumo (España). Real decreto 1301/2006, de 10 de noviembre, par el que se stablecen las normas de calidad y seguridad para la donación, la obtención, la evaluación, el procesamiento, la preservación, el almacenamiento y la distribución de células y tejidos y se aprueban las normas de coordinación y funcionamiento para su uso en humanos (Ministry of Health and Consumption (Spain), decree 1301/2006 of 10 November, by which norms of quality and safety were established for the donation, collection, control, processing, preservation and distribution of cells and tissues and norms for coordination and operation for their use in human beings were approved). *Boletin Oficial del Estado* 2006; 270: 39475-39498.

173 www.fcarreras.org/en/redmo-bone-marrow-donor-registry_701.

174 www.jcarreras.com/funda.htm.

in collaboration with the Register and the blood banks, coordinates the collection and the distribution of marrow and of cord blood. Still on the basis of this decree, if a unit of cord blood collected for autologous use turns out to e compatible with a person who needs a transplant, it will turned to be used for the transplant and the family of origin will be reimbursed for the expenses they have sustained for the preservation. This condition has had the effect that the majority of Spanish families seeking autologous preservation have recourse to export for preservation abroad.

The first independent bank of cord blood established after the entry into force of the decree 1301/2006 is VidaCord, which allows preservation in three possible locations: the Alcalá de Henares (council of the autonomous community of Madrid), at Nottingham (through Future Health Technology) and at Cracow (at the Polish Stem Cell Bank - Polski Bank Komórék Macierzystych). At present in Spain there are in operation numerous commercial bio-banks: Celvita España, Cryo-Save España, Future Health Technology, Ivida, Secuvita, Sevibe Cells, Smart Cells España, Stem Cell Banco de Células Madre España.This normative regulation makes Spain the country in Europe with the highest number of private banks, even though it is presently in a state of financial crisis.

*Switzerlan*d. There are two non-profit bio-banks for allogeneic preservation of cord blood at Basel and at Geneva. They operate in departments in local university hospitals and under the control of Swissmedic, the Swiss Institute for Therapeutic Products. The national register of the Blood Stem Cells Foundation (Fondation Cellules Souches du Sang) is responsible for the international exchange of blood for transplant. Within this system the specialist commission, Swisscord, operates; this consists of representatives of registers, experts in haematology, gynaecology, laboratory medicine and transfusions, with the task of establishing general policies concerning preservation of cord blood and transplants. Dedicated preservation is possible when there are indications for transplant for a brother.

Private bio-banks operate in the country, the chief of which is Swiss Stem Cells Bank.

III. BIOETHICS COMMITTEES AND INTERNATIONALS NETWORKS

Regulatory attention to the theme of cord blood banks is also attested by the fact that, in recent years, the National Bioethics Committees of many nations have dedicated specific documents to this question.[175] Such committees judge autologous preservation not to be useful, in the light of present scientific knowledge and to be damaging for the system of public donation (even if some members of these committees have expressed themselves personally in the opposite sense).

An important role in the organisation of cord blood banks is played also by the international networks. In 1994 the European cord blood banking group was established, with the aim of standardising and coordinating at the European level procedures for the collection and preservation of units of blood, of defining ethical and legal guidelines for the use of blood from the umbilical cord and of facilitating international cooperation in this sector. In 1995 the European Blood and Bone Marrow Transplantation Group (EMBT) set up the group EUROCORD, supported by the European Union, with the aim of studying the results of transplants of cord blood. For this purpose it established a specific European register of patients treated with transplants of cord blood with the aim of comparing results obtained from those patients who were treated with bone marrow transplants or with haematopoetic stem cells derived from peripheral blood. At present EUROCORD works on behalf of the EBMT, includes also non-European centres (over 180 centres in 35 countries) and collaborates with the American register CIBMTR (Center for International Blood and Marrow transplant research) in the sharing of information, above all with the purpose of avoiding the duplication of data reported. EUROCORD works in close contact with EBMT and NETCORD, for the purpose of collecting clinical data and of following patients who

175 In Europe the national committees of the following countries have expressed themselves on this question: Austria, Belgium Cyprus, France, Greece, Ireland, Italy.

have had transplants, whether inside Europe or outside of it. In 1998, finally, NETCORD arose, an international organisation with the aim of creating an international register of units of cord blood and of developing shared procedures for the collection, preservation and use of cord blood, for the purpose of maximising clinical use of banks of cord blood. Within NETCORD NetCord-FACT (NetCord Foundation for the Accreditation of Cellular Therapy) operates, which, since 2000, has promulgated the International standards for the Accreditation of Cord Blood Collection, Processing, Testing, Banking, Selection and Release (last revised in 2006). At present there exist 18 banks of cord blood accredited by NetCord-FACT in 12 different countries and more than 40 are waiting to obtain accreditation.

In the main European nations non-profit public institutions are also operating for allogeneic collection of cord blood, with procedures of voluntary donation.

APPENDIX

Controversies on the timing of the clamping and cutting of the umbilical cord at birth, with particular reference to the collection of cord blood for the donation of stem cells.

Since more than ten years a growing interest in the collection and cryo-preservation of stem cells present in the blood of the umbilical cord at birth has been registered. Considered in the past as waste material, umbilical cord is now widely used for transplants for some haematological and metabolic pathologies. In fact, the key features of this material lie in their high content of haematopoetic and mesenchymal stem cells, with some endowed of embryonic-like characteristics, and in their reduced capacity to provoke intense immune reactions in recipients. It is for this reason that they offer notable advantages for transplants into subjects compatible, children as well as adults, with respect to those derived from the bone marrow. Thus, an international network of public banks has been established for the collection, categorisation and cryo-preservation of cord stem cells with the aim of donation for altruistic and humanitarian purposes. Interest in this collection, by virtue of the constant and insistent megaphone of the media, has spread far beyond scientific circles, to the point of creating among the public the expectation of a "health supplement", to preserve and eventually to use in the future for the newborn himself or for members of his/her family, in reparative or regenerative cellular therapies, with the prospects and the hopes that progress in scientific research in biology and in medicine might be able to offer in the future. Thus, innumerable private banks have been established internationally, which, for unlimited periods of time and upon prior payment of sums of money payable in rates according to time, preserve the cord blood of newborn babies, which remains at the disposition of families for a hypothetical, future "dedicated" use.

Among the innumerable questions which the scientific literature has produced on this theme, one which is not to be under-estimated is that which concerns the timing of the clamping and of the cutting of the umbilical cord at birth, in relation to the well-being of the newborn "donor" himself.

It seems particularly appropriate and relevant to draw attention here to the scientific and ethical contributions which some authors have published on this specific question in recent years, especially that of José Luis Diaz-Rossello (2006), among the first to raise this question.

In the introductory part of his article, this author concentrates upon some historical references, up to 500 years ago, in order to demonstrate how important, going back into the past until now, the timing of the closure or clamping and the cutting of the umbilical cord at birth has been, in order to ensure the hemodynamic, respiratory and haematological well-being of the child just born. The attention of doctors in the past to this matter was due essentially to the fear that an interruption of newborn-placental blood-flow which was too precocious might constitute an element of risk for the health and the well-being of the newborn baby himself and, therefore, they tended to wait a few minutes before separating him from his placenta and that is to say the time to allow for a regular initiation of his respiratory function. Nowadays, in comparison with the past, the problem is posed with greater emphasis, given that the tendency is to clamp and cut the umbilical cord immediately after the expulsion of the foetus in a natural birth and after his extraction in a Caesarean section. It is done that way in order to obtain the maximum number of stem cells, destined for storage and donation. These could be used for eventual cell therapies, in cases of blood tumours or of other haematological and metabolic pathologies, of children or adults who are compatible. They could also be used for the purpose of research in the view of possible future uses for extra-haematological pathologies, either in regard to the newborn child himself in the course of his future life (autologous transplant) or of his blood relatives or of subjects extraneous to the family, but who are compatible (allogeneic transplant).

In normal conditions, according to the author, after the birth of the foetus, it is advisable to close and to cut the umbilical cord after the newborn has begun his regular respiratory function, after he has been placed upon his mother's abdomen and therefore at a level above the placenta still inserted in the uterine cavity, when the umbilical cord stops pulsating and when the cord vessels go limp. In fact, ligature which is premature with regard to these timings risks depriving the newborn baby of a considerable volume of blood

and provoking a condition of anaemia. On the other hand, the fact cannot be ignored that delayed ligature risks producing actually in the newborn baby a true policitaemia together with hyper-bilirubinaemia, because of the resulting excess of circulating blood cells. On the basis of this consideration, the author presents a series of data from the scientific literature, while recognising that all the elements, which could be relied upon from studies conducted ad hoc as to the real consequences of the timing of the closure of the cord vessels either for the newborn or for the mother, are not available.

In recent times, apart from the question of a "good" harvesting of cord blood cells, the tendency of early clamping of the umbilical cord has prevailed for at least 5 reasons, 4 of which are in favour of the newborn and 1 in favour of the mother, and they are; to avoid policitaemia and hyper-bilirubinaemia, to entrust the newborn to the neo-natal specialist as soon as possible, to obtain cord blood quickly in order to measure the pH and to undertake haemogas analysis, to place the newborn on the mother's abdomen and to initiate the sucking of the breast, thereby promoting early bonding, and, finally, to speed up the separation and expulsion o the placenta, with the aim of avoiding in the mother abundant post-partum uterine bleeding. Nevertheless, the author lists a number of reasons according to which the newborn would draw benefit from a delayed clamping of his umbilical cord, in terms of iron and therefore haemoglobin reserves, necessary for his normal development in the months succeeding birth. He lists data from the literature, which would show that a wait of 120 seconds benefits the new born, especially if he is low in weight or in case of maternal anaemia. This would reduce the need for a transfusion because of anaemia or hypotension and would avoid post-natal intra-ventricular haemorrhages.

The early cutting of the umbilical cord, with the purpose of donation, when the cord vessels are still beating and full of foetal-placental blood, does not take into account the interests of the newborn "donor", but is directed to the advantages which might derive for that child or that adult who would benefit from the transplant of the stem cells contained in that cord. Despite the pressing recommendations of the International Federation of Paediatricians and of Obstetricians and Gynaecologists, who have called for early clamping of the umbilical cord at birth to be avoided, no follow-up, and

hence no rigorous application of these directives, has ever been registered, nor has this matter ever been included in the official bioethical documents present in the Institutes of Medicine and in the European Committee of Bioethics. In June, 2006, an official declaration, emanating from the Royal College of Obstetricians and Gynaecologists, complained about the habitual and excessive speed with which the staff in the delivery room clamp the umbilical cord at birth, for the purpose of obtaining a specimen rich in cell elements, so as to render as efficient as possible a transplant to a possible recipient, whether a child or an adult. Furthermore, the Royal College warns the staff to avoid interfering by means of procedures which are inadequate on the physiology in the third stage of birth, that is to say on the after-birth.

In the request made to parents that they donate the blood of the umbilical cord of their own children at birth, the difference is not specified and therefore does not appear in the document of informed consent, either of public banks or of private banks, between the "natural" content of the cord blood and its content in the case of early clamping, in relation to the presence of the iron destined for the newborn in both cases, with the deprivation, as a consequence, of this vital element in the case of the immediate closure of the umbilical cord at birth. If the mother or both parents were to be aware of this difference, the author concludes, they would still give consent to the donation, but only on condition of not damaging the baby. They would therefore ask to the ligature of the cord according to the physiological time factor. In this case, altruism cannot do other than respect the health and well-being of the donor, limiting itself to ceding only the residual cord blood and certainly not at the risk of damaging more than is necessary the baby himself at his birth.

Moreover, it needs to be said that in the collection of cord blood a common and well-established criterion must be included with regard to pregnancies destined for donation. This looks for the physiological unfolding of the pregnancy with a birth after the 34th week of gestation. It excludes from collection those pregnancies with foetal malformations, a gestational age below 34 weeks, maternal fever during labour, rupture of the membrane of more than 12 hours, foetal suffering attested by the presence of meconium in the amniotic liquid and cardiotocographic abnormalities, delay in intra-uterine growth and neo-natal Apgar below 6 (Mancuso & Perillo, 2007).

Therefore, not all pregnancies are candidates for possible donation, but only those which meet these criteria.

In the premature newborn delayed clamping of the umbilical cord is necessary, for the purpose of permitting a prolonged perfusion of blood from the placenta ("placental transfusion") to the baby before interrupting the cordonal blood flow. This way a physiological normovolemia is reached and a considerable transfer of iron (circa 30 mg) is obtained at birth (Kinmond et al., 1993). In the newborn brought to term, waiting for 2 minutes before clamping is recommended by Hutton & Hassan (2007) from a review of the literature. These authors underline the fact that the neo-natal policitaemia and hyper-bilirubinaemia which follow do not represent fundamentally an element of risk, but rather a useful reserve of iron, sufficient for the subsequent 6 months, apart from preventing anaemia for at least 3 months, especially in developing countries, where hypo-sideraemia is endemic. The authors conclude that, for the purpose of obtaining maximum neo-natal benefit, further research is needed to establish the optimal times for clamping the umbilical cord at birth, deducing it from the determination of the minimum time required for an optimal placental transfusion The review of Chaparro (2011) underlines the importance of the iron reserve in a healthy newborn, in which he estimates that the total quantity of this element obtained from the mother at the term of gestation runs at about a normal value of 75mg/kg of weight, when the interruption of the placental haematic flow takes places three minutes after birth. For the newborn, in fact, the need for a high concentration of iron with respect to the adult (55mg/kg) is necessary for his normal development, taking account of the fact that maternal milk is poor in this mineral. The author concludes, reminding staff assisting in the delivery room not to be in a hurry to clamp the umbilical cord, to listen to the recommendations of nutritionists, and to adopt ways of conducting themselves when assisting at births which show that they are more aware.

A recent article by Swedish authors published in the BMJ (Andersson et al., 2011) reports a controlled clinical study on 400 newborns at the term of low-risk pregnancies, in which the times of clamping the umbilical cord were randomised, early (10 seconds or less of birth) and late (180 seconds or more of birth), with the primary objective of verifying at a distance of 4 months

from birth haemoglobin and iron status (serum ferritin level). The secondary objective of that study was to find out whether or not there was a difference between the two groups regarding postnatal respiratory symptoms, polycythaemia, hyper-biliruminaemia, or need for phototherapy. Two days after birth, the newborns with late clamping presented a prevalence of anaemia clearly inferior with respect to that present with early clamping. while haemoglobin values at a distance of 4 months turned out to be equal between the two groups, even though the serum ferritin levels were significantly lower in babies who had undergone early clamping. In both groups, however, differences in respiratory symptoms and in symptoms of policitaemia and hyper-biliruminaemia were not shown. Based on these data, the authors concluded that early clamping would bring to the newborn a risk of post-natal anaemia with a low level of ferritin, expressing a reduced iron reserve, up to 4 months after birth. Since hypo-sideraemia, even without anaemia, could be associated with disturbances to development, later clamping is advisable not only in economically depressed areas, but also in those areas where a low prevalence of sideropenic anaemia has been registered. Besides, it is to be underlined that the authors have not reported real immediate and/ or delayed negative effects of early clamping on the health of the babies studied.

The controversy on the time of clamping of the umbilical cord at birth remains an open question and it is one which, today, is even more pressing, given the need to obtain a high concentration of stem cells, whether in donation with an altruistic purpose or in banks with a "dedicated" purpose, destined in the first case to public banks and in the second to private banks. The fact is to be stressed that a long wait before clamping produces an almost total emptying of the umbilical cord, which is reduced to a volume not exceeding 15 millilitres and which, therefore, is no longer usable for the purposes of transplant. In normal conditions, after a wait of at least 60 seconds before clamping, with the placenta still inserted into the womb, it is possible to collect a quantity of cord blood up to 100 millilitres and the same amount can be obtained after the after-birth by means of "milking" the cord, compression of the placenta and making one or more punctures in the cord vessels. These quantities are considered suitable and sufficient for

donation to a baby or an adult, in the latter case after expansion in vitro or by joining together the contents of different cords in a double or triple donation (Mancuso & Perillo, 2008).

It remains a fact that research on cord stem cells produces every day results which are more and more convincing, not only on the actual use of the stem cells in haematological and metabolic pathologies, etc., but also in terms of the role that cell therapies may have in a future panorama of medical applications. For this reason staff dedicated to pre-natal supervision and to assistance at delivery are called upon more and more to assume the role of being educators and providers of information with respect to those who are in gestation and to families, encouraging and preparing for the collection of this precious and potentially curative material, either for donation or perhaps even for dedicated collection, when research is able to demonstrate its usefulness (Waller-Wise, 2011). It seems highly appropriate to establish canons of behaviour for staff attached to the deliveries, and not only those for mother in gestation who have expressed the wish to donate the blood of the umbilical cord of their own child at birth.

According to the data discussed by Navarrete at the International Congress on Umbilical Cord Blood (Rome, 27-29th October 2011), more than 600,000 specimens of cord blood are presently stored in public centres of the highest quality in the world (over 150 banks), without counting private banks. No condition of a serious pathology occurring in newborns after the early clamping of cords used for the purpose of donation has ever been registered or described. It can be rationally hypothesised that in none of the authorised centres could clamping have occurred more than 60 seconds after the expulsion of the foetus. All the specimens preserved in public banks have been categorised and, therefore, are ready to enter into an international network for use for cellular therapies and, as of today, about 26,000 transplants have been effected in the world, more than 4,000 in 2010 alone, a third of these being in babies and the rest in adults and all with therapeutic success.

In conclusion and in the light of the data in our possession, it seems opportune to furnish parents of the newborn donor with information which

is complete, adding to the form requesting informed consent the following points: that staff working as assistants in the delivery room should not be in a hurry to interrupt the placental flow in the interests of the health and well-being of the newborn, that the timing, in seconds, of the clamping of the cord should be registered on the clinical chart, in any case this should not be less than 60 seconds, that parents be registered as bone marrow donors as the same time as the donation from the newborn and that it would be appropriate to undertake a haematological check on the newborn at 4 months after birth, to exclude the risk of anaemia and of a grave diminution of his reserves of iron.

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GLOSSARY

Umbilical cord banks

Banks for preserving umbilical cords are real and proper 'banks' where the units of cord blood are preserved. After being collected in the delivery room, the unit of cord blood is sent to the bank, where it is subjected to a series of specific tests to assess its suitability for preservation and to define its immunological characteristics, with the purpose of the analysis of compatibility between donor and recipient. The first bank for the preservation of cord blood arose in New York in 1991 at the initiative of P. Rubenstein. Between 1992 and 1993 there arose several public banks also in Europe. The proliferation of cord banks throughout the world has led to the creation of various networks between the banks, both at national level and internationally. At present the Bone Marrow Donors Worldwide (BMDW), set up in 1988 at Leiden (Holland), constitutes the largest international register of blood marrow donors and of banks of cord blood.

Stem Cells

Stem cells are progenitor cells with a high potential to proliferate, capable of renewing themselves (that is to say, capable of reproducing daughter cells equal to themselves) and of generating one or more specialised cellular types (that is to say, capable of giving rise to all the specialised cells which constitute the various tissues and organs). A fundamental role seems to be played by the so-called 'niche', that is of the micro-environment of the stem cell *in situ*; this micro-environment would keep the cells is the state of *stemness* by means of biochemical signals, which inhibit their maturation. In the human being so far four sources of stem cells have been identified: 1) embryonic stem cells (derived from the internal cellular mass of the blastocysts), 2) germ cells derived from the foetus, 3) stem cells from the umbilical cord, 4) adult stem cells (identified in the bone marrow, the pancreas, the bone, cartilage, the liver, the skin, the nervous system and in adipose tissue).

Haematopoietic stem cells

Haematopoietic stem cells are cells which are capable of giving rise to all of the corpuscular elements of the peripheral blood (red globules, white globules and platelets). These cells are able to regenerate the marrow environment in all those cases where it has been damaged following pathologies, accidental exposure to ionising radiation or by chemo- or radiotherapy. for the treatment of tumour pathologies. They are present in the bone marrow (where they constitute 1.1-3% of the population of the cells present), in peripheral blood (0.01- 0.1%) and in cord blood (0.1- 0.4%).

Mesenchymal stem cells

Mesenchymal stem cells are cells which are capable of giving rise to adipose tissue, cartilage and bone. They are contained within the stroma of the marrow. They constitute a population of pluripotent cells and so, if appropriately directed, can give rise to cells with the characteristics of varying tissues.

Endothelial progenitor cells

Endothelial progenitor cells are stem cells which originate in the marrow, and which are involved in the process of the repair of the endothelia and in the processes of angiogenesis.

Autologous preservation (for autologous use) of cord blood

Preservation is defined as being for autologous use when the cord blood is preserved for the newly born child to whom it belongs (or for a member of his family). The expenses of the collection and preservation of the cord blood are borne by the family. In most cases, autologous preservation is seen as a form of life insurance, but it risks generating a product which is destined to remain unused in the vast majority of cases.

Allogeneic preservation (or for allogeneic use) of cord blood

We speak of allogeneic collection and preservation when the blood from the umbilical cord is donated to be placed at the disposal of people as a whole. The donation is voluntary, gratuitous and anonymous. Its collection and preservation do not involve any burden for the donor or for his or her family.

Dedicated preservation (or for dedicated use) of cord blood

Dedicated collection and preservation of cord blood occurs in the case where the umbilical cord is dedicated to a relative who is compatible, generally to a brother or a sister, who is affected by a pathology for which a therapeutic treatment is indicated which envisages the use of haematopoietic stem cells. Its collection and the preservation do not involve any burden for the donor or for his or her family.

INTERNATIONAL ASSOCIATIONS AND NETWORKS

BMDW - Bone Marrow Donors Worldwide

http://www.bmdw.org

CIBMTR - Center for International Blood and Marrow Transplant Research

http://www.cibmtr.org

EBMT - European Blood and Marrow Transplantation Group

http://www.ebmt.org

EUROCORD

http://www.eurocord.org

NETCORD

http://www.netcord.org

NetCord-FACT (Net-Cord Foundation for the Accreditation of Cellular Therapy)

http://www.factwebsite.org