National Consultative Ethics Committee for Health and Life Sciences

OPINION N° 117

Use of stem cells derived from umbilical cord blood, the umbilical cord itself and the placenta; their storage in biobanks. Ethical issues.

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Summary

Introduction

For over twenty years, the use in human medicine of cord blood stem cells[4] which are collected without harm ensuing to either the mother or the new born child, has contributed to notable therapeutic and scientific advances in the field of bone marrow allografts.
The umbilical cord connects the foetus to the placenta via arterial and venous blood vessels containing foetal blood. At birth, once arterial pulsation has ceased and the cord is clamped, the cord blood[5] can be collected from the blood vessels. Using specific and strict precautions, the stem cells are separated from the rest of the blood and stored in various kinds of biobanks[6]. Biobanks storing such samples with a view to the transplant of haematopoietic marrow raise as yet unsolved ethical issues in some cases, particularly concerning those biobanks offering solely autologous haematopoietic stem cell transplants (reserved for the newly born child's own use), but also when intrafamilial allografts between siblings are intended.

There are two angles from which the question of biobanks can be viewed and they are not commensurable. On one level, the nature of storage[7], — autologous, for family or for public allogeneic use — is compared and analysed. On another level, the public or private nature of funding and operating the biobank is discussed[8].
More recently, the attention given to stem cells contained in the cord lining[9], in the placenta and placental annexes, has given rise to scientific publications setting out their novel therapeutic potential. There is a section in the median area of the cord, called Wharton's jelly[10], containing a large number of mesenchymal stem cells whose potential for regenerative cellular therapy has been the subject of recent research. The creation of mesenchymal stem cell collections, or even of biobanks for the purpose of fundamental and applied research on cells derived from that area instead of from cord blood, now seems to be a feasible or even propitious option.

Ten years after the publication on December 12th 2002 of its Opinion n° 74 on "Umbilical Cord Blood Banks for Autologous Use or for Research", the National Consultative Ethics Committee for Health and Life Sciences (CCNE), decided to discuss the ethical impact of facts and findings occurring in the meantime, as analysed below:

- We know today that UCB (Umbilical Cord Blood)[11] units can be a useful substitute for allografts of haematopoietic stem cells harvested by multiple medullary bone punctures under general anaesthesia on live donors, related or unrelated to the recipient. These UCB units could become an even more frequent alternative to haematopoietic bone marrow if greater quantities of them

4 See the note in Annex 1 on stem cells in general.

5 Arterial blood shunted by the foetal heart carries deoxygenated blood and foetal metabolic waste away from the foetus. This blood is purified and reoxygenated in the placenta by the maternal circulatory system; it returns to the foetus via the umbilical vein. It contains a large quantity of foetal stem cells, in particular haematopoietic cells capable of regenerating the various kinds of blood cells. Therapeutically, it is extremely useful when it is transplanted as a substitute for defective or destroyed haematopoietic bone marrow, irrespective of the cause of marrow failure.

6 See the note on cord blood-derived stem cell biobanks (Annex 2)

7 This is the purpose of the draft law N°1938, dated 29/09/2009, proposed by Daniel Meslot, MP.

8 The possibility of allowing the establishment of private cord blood biobanks in France was considered in recommendation 4 of Report N°79, dated 04/11/2008, presented by Marie Thérèse Hermange in the name of the French Senate's Committee for Social Affairs.

9 See the note on mesenchymal stem cells (Annex 3).

10 Named after the man who first described it in the 17th century (see Annex 3 of this report).

11 The cord blood units serving as a possible substitute for marrow haematopoietic stem cell grafts are usually designated by the name of 'UCB units'.

were available as well as a broader range of HLA phenotypes[12].

- Despite progress in the last five years, in particular under the aegis of the *Agence de Biomédecine*, French biobanks with stocks of UCB units dedicated to allografts as an alternative to haematopoietic bone marrow are still too scarce and they do not contain a sufficient supply of stored UCB units[13].
- If at least partially HLA histocompatible haematopoietic stem cells are to be used instead of bone marrow for allografting, then a large number and a great variety of UCB units with different HLA phenotypes must be made available.
- Biobanks, both in France and abroad[14], need certain UCB units with rare HLA phenotypes specific to certain ethnic groups living in France so that haematopoietic stem cell transplantation for all kinds of indication can be performed if required.
- Since there is currently a shortage of UCB units in French biobanks, grafts have to be imported from other countries, at very high prices, much above the cost of this identical technical procedure for procuring them in France.
- New indications for the graft of haematopoietic stem cells have been recently discovered for inherited genetically transmitted haemoglobinopathies. The sibling-to-sibling graft of HLA-matched haematopoietic stem cells is now used for treating — and curing — such conditions. The patient's quality of life is much improved and presumably the method will be more economical in the long run than treating haemoglobinopathies and their complications.
- In agreement with a health care policy setting a priority on a national anti-cancer programme, (*plan Cancer*), treatment for malignant haemopathies, with the side effect of destroying the haematopoietic bone marrow, requires a supply of haematopoietic stem cell grafts to alleviate medullary aplasia[15] and create an anti-leukaemia immune system (graft-versus-leukaemia effect, acronym: GVL). The reinfusion of haematopoietic stem cells provides better chances of survival for the patient and also turns out to be less costly than treating recurrent leukaemia relapses. On all counts and in terms of patient welfare, there is a case for making more widespread use of these medical advances.
- UCB units biobanks, however they are funded, should base their priorities on solidarity and the possibility of national and international exchanges so that, whenever feasible, allogeneic HLA-matched bone marrow transplantation can be made to happen.

Could both kinds of allogeneic biobanking entities, those for use within the family and those with a dual role, family and solidarity, be set up[16] if the competent authorities readjusted public health policies?

Moreover, in view of events since 2002:

A critical examination of our manner of thinking and of our current clinical practices has become all

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12 'Human Leucocytes Antigens' (HLA): See Annex 4 for an explanation of the HLA system.

13 In 2012, the need for allografts in France to satisfy the requirements of oncohaematologists in the indication of bone marrow grafts, after aplasia is induced for malignant haemopathies, is not covered solely by grafts from France, be they supplied by related or unrelated live volunteer donors or by UCB units.

The number of UCB units registered and stored in our public biobanks is insufficient to satisfy the growing clinical demand due to an ever greater number of indications, of all descriptions, for bone marrow allografts.

The curves plotting the number of requested marrow allografts each year are increasing faster than those plotting the number of available allografts from all sources.

14 63% of UCB units grafted in France come from other countries.

15 Aplasia is the state of the haematopoietic bone marrow when it ceases to produce stem cells and blood cells, resulting in anaemia for lack of red blood cells, infections because of white blood cell deficiency and bleeding due to missing platelets.

16 See the note on various kinds of UCB biobanks (Annex 2).

the more necessary because of recent research concerning stem cells contained in the umbilical cord itself. Scientific investigation of non-haematopoietic stem cells, derived from the mesangial area of the cord lining and from the placenta (these are cells which can be used for fundamental and applied research)[17] has made considerable progress. The products of the "afterbirth[18]", after expulsion, can be used to harvest mesenchymal and endothelial stem cells from the cord blood vessel walls, in regulatory conditions which remain to be defined. The abundance of these cells and their properties are such that there is growing interest in using other cell products derived from the cord itself and from the placenta for fundamental and applied research, which could well lead to reasonable hopes of making progress in regenerative medicine.

I - Medical and scientific value of umbilical cord blood: State of the art 2012

In France, towards the end of the 1950s, Georges Mathé and his co-workers pioneered the first attempts at grafting cells extracted from haematopoietic marrow. The cells for injection were drawn from bone marrow samples harvested by multiple bone punctures on live volunteer donors. The medullary cells were injected to patients with medullary aplasia after they had undergone accidental and potentially lethal civilian nuclear irradiation. This therapeutic trial, which was published in scientific journals, showed that haematopoietic bone marrow transplantation was technically feasible.
Later, a number of patients suffering from severe haemopathic conditions, mainly cancerous, were treated effectively by grafting haematopoietic stem cells to alleviate haeemapoietic marrow aplasia.
Although this is an extremely useful technique, it is physically very taxing for both recipients and donors. Recipients will be very fragile due to anti-leukaemia chemotherapy and will need to be placed in a closed sterile hospital unit as long as they are in a state of medullary aplasia, since they no longer have any white blood cells to defend them against transmissible infections (viral and bacterial). As for the healthy volunteer donors, they must undergo general anaesthesia and more particularly, multiple bone punctures in order to aspirate marrow samples. These punctures have their drawbacks, among which pain, as donors emerge from anaesthesia[19].

Today, haematologists are aware that for a graft procedure to prove successful and normal haematopoietic marrow to be the outcome, depends to a high degree on the number of haematopoietic stem cells present in the donor's bone marrow samples. As a result, repeated punctures are performed under anaesthesia until haematopoietic stem cells are collected in sufficient quantities to ensure successful transplantation.

The discovery that such haematopoietic stem cells were present in umbilical cord blood has led to the practice of "familial" allogeneic transplantations of this blood collected at birth. It was in France, in 1988, that Eliane Gluckman and her team, pioneered the first familial allogeneic graft for the treatment of an elder brother with congenital Fanconi's anaemia, a serious condition, highly life-threatening even before the age of puberty. The HLA phenotype of the neonate's cord blood was identical to the recipient's. The long term success of this first therapeutic trial is now confirmed.

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17 See the note in Annex 3 on restorative medicine, cell therapy and mesenchymal stem cells.

18 The word "afterbirth" is used here to describe the entire placenta, membranes and the rest of the umbilical cord emerging from the uterine cavity a short while after birth. Also referred to as placental expulsion.

19 There does exist however another method as a substitute for bone puncture which consists in giving donors doses of special growth factors (G-CSF) to stimulate a significant proliferation of haematopoietic stem cells in their peripheral blood stream. These can then be harvested, in greater numbers than through repeated bone marrow punctures, by intravenous blood sampling, from which they are extracted by separation until a sufficient quantity is acquired. The blood, minus these haematopoietic stem cells, is then reinjected to the donor.

Since this global premiere, a great number of haematopoietic stem cell grafts have been performed world-wide, using allogeneic UCB units preserved in biobanks and duly registered for HLA matching.

The types of haematopoietic stem cell transplant procedures currently in use for haematological indications are the following:

- **Autologous grafts** involving the use of stem cells harvested from the patient's own peripheral venous blood for cases of myeloma and lymphoma[20].
- **Allogeneic grafts** using haematopoietic stem cells from the bone marrow of **live volunteer donors**, related or unrelated to the recipient, with so-called "HLA-identical" phenotypes. The allogeneic grafts concern patients whose leukaemia involves lymphoid and granular white blood cells (polynuclear and monocytes). Such patients will have been given anti-cancer drugs to induce remission and bone marrow aplasia.
- Substitution **allogeneic grafts** using **UCB units**. They represent some 20% of the total number of haematopoietic stem cell transplantations, but this percentage could increase in the long term, in the absence of living donor siblings with perfect HLA histocompatibility, on the condition that a greater number of UCB units become available in biobanks, particularly for rare HLA phenotypes.

Using UCB units for haematopoietic stem cell allogeneic grafts has the advantage of avoiding the drawbacks (due to general anaesthesia and repeated bone punctures) of medullary haematopoietic stem cell harvesting from a healthy volunteer. Nevertheless, haematologists still prefer this type of medullary transplant for complex, but pertinent, histocompatibility reasons, although results as recorded in international registries, for haematopoietic UCB unit derived grafts, show a high success rate[21]. On average, four years after the graft of UCB units their outcome is 56% in allogeneic procedures following chemo- and radiotherapy for malignant haemopathies, and 92% in grafts for inherited congenital haemoglobinopathies.
These success rates with UCB unit grafts do not differ a great deal from those arrived at with haematopoietic stem cell grafts following bone marrow punctures.
In the circumstances, whenever possible, so called HLA-identical UCB units should be a medical priority in order to implement the principle of avoiding harm to healthy volunteers.
However, the concentration of haematopoietic stem cells in UCB units is still a pertinent cause for concern on the part of haematologists in the specific context of bone marrow substitution. In some cases, this may lead to the injection of two or even three "HLA-identical" units at the same time. If this became general practice, a far greater number of UCB units than are in fact available at this time worldwide would have to be collected.

As a result, many countries are proceeding increasingly frequently, year on year, with the harvesting and cryopreservation of cord blood with a view to haematopoietic stem cell **allogeneic transplants**[22].
At the same time, cord blood biobanks have been created worldwide to store and distribute these UCB units.
A large number of them are public; many are private but are non-profit organisations. All these

20 After aplasia induced by chemotherapy or radiotherapy to destroy all malignant cells not involving granular white blood cells (polynuclear cells and monocytes), the haematopoietic marrow begins to regenerate, partially and slowly. Specific growth factors (G-CSF) are then injected at the start of medullar self-regeneration. These growth factors induce haematopoietic stem cells to emerge from the marrow in the early stages of regeneration into the peripheral blood stream where they are collected intravenously after selection excluding other blood cells.

21 Meaning a large proportion of patients having received allogeneic haematopoietic stem cell grafts and living with functional transplants capable of normal haematopoiesis.

22 Gluckman E.: Milestones in umbilical cord blood transplantation. Blood Rev. 2011; 25(6):255-9.

allogeneic banks have in common that they comply with the same standards for collection and supervision, including on a mandatory basis the precise determination of the HLA phenotype.

The global network of healthy volunteer marrow donors totals some 18 million people, which means that, for an aplastic leukaemia patient, it is always possible to locate several harvestable donors in good time, and select one of them, depending on availability and who has the best histocompatibility.
In comparison, an inventory of the global network of UCB unit biobanks reveals a figure of approximately 600,000 UCB units. The available choice of HLA-identical UCB units for a given recipient is therefore infinitely smaller than the one offered by the network mentioned above.
These UCB units however, are available at all times for allogeneic transplants, unlike volunteer donors who may not be free when they are needed. They are stored in various kinds of biobanks which all have in common that they are intended for use by the community and for allogeneic transplants.
Over 20,000 UCB units have already been distributed worldwide[23], primarily for the treatment of children but also, increasingly, for adults with life-threatening persistent medullary aplasia.

Public UCB unit biobanks in France must comply with the ethical principle of justice that *"the solidarity which underlies the harvesting and use made of products of the human body since the enforcement of the laws on bioethics, has as a necessary consequence that donation is anonymous, free of charge and undirected[24]".*

More than ever at this time, as is pointed out in CCNE's Opinion n° 101[25], *"The pertinence of therapeutic action must be improved by reducing to a minimum the disproportion between* ***effectiveness*** *and the scale of resources that are put to use."* To achieve this, it would certainly be appropriate for public services who are technically competent to do so, such as the CNAM (*Caisse Nationale d'Assurance Maladie* - National Health Insurance Fund), to undertake economic studies comparing, for example:

- costs ensuing from the import of UCB units and those ensuing from an increase in the production and storage of UCB units in France,
- costs ensuing from the graft of haematopoietic stem cells harvested from healthy volunteer donors and those ensuing from the harvesting and storage of UCB units, taking into account possible side effects (GVL, GVH) and outcomes in terms of patient comfort, quality of life and survival time.
- costs ensuing for allogeneic grafts of haematopoietic stem cells for leukaemia with a confirmed graft indication to those ensuing from the treatment of leukaemia relapses when it was not possible to proceed with haematopoietic stem cell engraftment.
- costs ensuing from allogeneic marrow grafts for homozygous sickle-cell diseases to those

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23 Several studies published by oncohaematology centres have shown that the number, per unit of volume, of haematopoietic stem cells in cord blood is the most important factor for the engraftment of bone marrow to be successful, whereas a certain degree of HLA phenotype inadequacy between the UCB unit donor and the recipient may be acceptable without any great impact on the success of the procedure. For this reason haematologists are keen to see **quantitative** criteria for storage in biobanks applied **to UCB units selected for this purpose**.

In the last few years, however, it has become possible to secure good engraftment with adults, by injecting two or three HLA-identical UCB units, derived from different umbilical cords although the criteria for cellular density in each unit had been previously considered insufficient to enable satisfactory engraftment.

24 Marie -Thérèse Hermange in her explanatory introduction to her information report n°79 addressing the French Senate on 4th November 2008.

25 CCNE's Opinion N°101 "Health, ethics and money: ethical issues as a result of budgetary constraints on public health expenditure in hospitals", June 28, 2007.

ensuing from the treatment of sickle-cell anaemia and its complications throughout the life of a patient, including the consideration of comparative patient comfort.

To sum up this first chapter:

CCNE considers today that there is no call for substantial change to its Opinion N°74[26] as regards its general economic thrust, its contents and recommendations insofar as they apply to cord ***blood*** harvesting.

This documented opinion had replied clearly, in the negative, to the question contained in the *Directeur Général de la Santé's* referral as to whether the development of private biobanks for autologous purposes and as a substitute for haematopoietic bone marrow by UCB units should be supported. As a consequence, private biobanks are now prohibited in France. The criticism denouncing deceptive advertising in this Opinion is still pertinent and, in fact, it should be voiced more strongly in today's context.

In their 2002 Opinion, CCNE emphasised however that: "*Science is always uncertain, but law can always be revised"*. This prudent position is now justified by the opportunities offered (see Chapter IV) by certain regenerative medicine practices, neonatal in particular, motivating a mitigation of several reservations voiced ten years ago.

II – Status of the placenta and annexes and harvesting their products

Traditionally in western civilisations, the placenta and the portion of the cord that remains attached to it after it has been cut at birth, become "res derelictae", meaning "things that were once part of the mother's body", but which will be "abandoned" by her after expulsion of "the afterbirth". This has as a consequence, including as a legal[27] consequence, that they be disposed of accordingly as medical waste involving a risk of infection (*déchets d'activités de soins à risques infectieux - DASRI).*

And yet, not so long ago, placentas and their annexes were collected from the maternity wards by third parties for industrial and commercial uses, some of which were medical (immunoglobulins in

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26 CCNE's Opinion N° 74, dated December 12, 2002, on "Umbilical cord blood banks for autologous use or for research":
- mentioned the existence of community UCB unit biobanks where the units were harvested by gravity from the clamped cord vein while the placenta was still within the womb; these biobanks were to be used for allogeneic marrow grafts, mostly for children.
- recommended that the authorities increase the number of maternity units where cord blood could be collected as well as the number and capacity of public banks and their coordination;
- raised the issue of lack of solidarity and justice as regards placental blood harvesting for purely autologous purposes. It criticised therefore the principle of cord blood biobanks created for solely "autologous" use and pointed out that the number of therapeutic indications for such blood collections was, at the time, minute;
- underlined that indications for the use of stem cells for regenerative autologous purposes, using non haematopoietic stem cells derived from cordon blood were still generally unconfirmed and were mainly relevant to research;
- allowed however that: *"Should scientific progress produce encouraging data in future, which is not the case so far, then political authorities will need to organise matters so that equal access to healthcare prevails, and so that the mismatch between selfishness and solidarity is reduced to a minimum.*" Scientific developments in the last ten years now fully justify CCNE's precautionary statement at that time since the paradigm has changed;
- furthermore, CCNE sounded a note of caution to the effect that if health carers and non medical staff in maternity wards were busy harvesting cord blood in the delivery room while the placenta was still *in utero*, this constituted a significant risk for the neonate and the birthing mother since health carers would be distracted from their primary task, i.e. assisting delivery, attending to the mother's immediate *post partum* needs and providing neonatal care for the new-born child.

27 In the delivery room, the placenta and its annexes, once their entirety has been verified, are placed in a special bin containing all the soiled swabs. All contents of this receptacle must be disposed of in compliance with the regulatory stream for "DASRI" (medical waste involving a risk of infection - *déchets d'activités de soins à risques infectieux),* so that they may be destroyed by controlled incineration.

particular) and others for the cosmetics industry[28], which was contrary to the way of thinking generally of CCNE's Opinions n° 21, 25, 77, and 93[29]. The practice, however, followed an ancestral principle that "abandonment" of a possession, in this instance the placenta and its annexes, means that it no longer belongs to anyone, and can therefore be appropriated by anyone without exclusion.

After delivery, a not inconsiderable amount of time (around 15 or 30 minutes) elapses before expulsion of the "afterbirth", following on from uterine muscle contraction expelling the placenta and its annexes from the uterine cavity. This event marks the final separation of the "afterbirth" and the mother.

During this time when the placenta, its annexes and the cord remain in the womb, they are still partially oxygenated by the mother's arterial blood flow to the placenta. They will become the "afterbirth" once they are pushed out of the uterus, but at this point they are still "*part*" of the mother's body, albeit with a foetal origin which cannot be dissociated from the neonate.
This interval may provide sufficient time for harvesting the foetal blood originating before birth and remaining in the cord blood vessels after the neonate's arterial blood flow to the placenta has stopped. This blood is still being partially oxygenated by the birthing mother via the placenta which is still *in situ*. The obstetrician or the midwife can collect it manually by puncturing the vein, or by provoking the flow of blood by gravity, when the cord is cut, out of the vein and the two arteries. Whatever method is chosen, it must be entirely aseptic and the blood stored in appropriate sterile containers provided by the *Etablissement français du sang (EFS)* (French National Blood Agency).

In France, one of the members of the medical team, already present in the delivery room and specially trained for this procedure, usually proceeds with harvesting. One of the healthcarers already operating must obviously be chosen for reasons of safety since the birthing area has to conform to strict rules of asepsis for the protection of both mother and child.
Having one of the active members of the medical team in the delivery room perform this harvesting procedure may seem to be in contradiction with their primary priority which is to look after the mother and the new-born child. No conflict of interest between harvesting cord blood (particularly if payment is involved) and the health caring attention owed to mother and child can be allowed to exist. Removing the existence of this contradiction, ethically patent, implies the funding of extra staffing in the maternity departments of licensed healthcare institutions to participate in the cord blood collection programme. Apart from satisfying ethical concerns, taking this course would help to motivate health carers involved in the programme and thereby increase the number of UCBs collected and made available in France.

The blood which is collected is then processed extemporaneously, outside the delivery room, by dedicated personnel whose task it is to separate by centrifugation the sediment layer (called "buffy

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28 *"When it is stated that the human body is not for sale and not on the market, the two statements are complementary : on the one hand, the human body or one of its components cannot be the object of a contract, on the other hand, it cannot be negotiated by anyone."* Which implies the absence of *payment*, the *not-for-profit character of subsequent operations*, *respect for the donor and the patient's best interests*.

Any concession, for example, by reason of the fact that blood is a renewable tissue and that limited withdrawal cannot be considered prejudicial, would undermine the rule ensuring the protection of human dignity.

If this principle was accepted for blood, all other tissues and organs could become items for trade.

CCNE's Opinion N° 25, dated June 24, 1991, mentions Opinion N° 21 of December 13, 1990 on the human body or parts of the human body not being used for commercial purposes.

29 CCNE's Opinion N° 21 on the human body not being used for commercial purposes, December 13,1990.

CCNE's Opinion N° 25 on "The application of genetic testing to individual studies, family studies and population studies. (Problems related to DNA "banks", cell "banks" and computerisation)." June 24, 1991.

CCNE's Opinion N° 77 on "Ethical issues raised by collections of biological material and associated information data: biobanks, biolibraries. March 20, 2003.

CCNE's Opinion N° 93 on "Commercialisation of human stem cells and other cell lines". June 22, 2006.

coat") containing white blood cells and platelets from the stem cells[30]. The cells present in this sample[31] are in the main rather large quantities of haematopoietic stem cells and a much smaller quantity of endothelial and mesenchymal stem cells (around 0.2%). The sample must then undergo rigorous biological examination, based on a consensual protocol, to check whether the cells are of a **quality** sufficient for therapeutic purposes, either predominantly haematological or regenerative[32]. Haematologists also want **quantitative** criteria[33] specifically required to form a UCB unit to be used as an allogeneic substitute for bone marrow.
Meanwhile, separate samples of small quantities of cord blood are collected for various biological analyses, first and foremost for HLA typing[34].
Admission to a public biobank, after a number of tests[35], is the final phase of the procedure, the total cost of which is very high.

Logically, harvesting blood from the vein or other cord vessels when the placenta is still *in situ*, is classified as a "donation" by the mother since the placenta has not ceased to be a "*part*" of her body. For the gift of cordon blood to be allowed and out of respect for her autonomy and maternal feelings in favour of solidarity and justice, her "informed" and written consent must be secured before labour begins. If the plan is to also harvest mesenchymal stem cells from the cord lining or from the placenta for fundamental or preclinical research purposes, it is also necessary to obtain the mother's specific consent, or at least a formal statement of non refusal, in the name of respect for personal dignity and of the human body, even though the cellular components involved were in fact originally belonging to the neonate.

It seems to be an exclusively French particularity that most collections of placental and foetal cord blood are performed in the delivery room by obstetricians or midwives, who are of course duly trained to do so, but while the placenta is still within the uterus.
As reported by Éliane Gluckman, in many other countries, cord blood harvesting as well as that of other placental products is generally done by dedicated personnel once the afterbirth has been delivered and in another place, separate from the delivery room. Before the afterbirth can be put to any use, the midwives must examine it very meticulously to make sure that it is entire, i.e. the whole placenta and all the annexes present to verify that nothing was left behind in the uterus. This is one of the medical staff's mandatory tasks; it requires a significant period of time during which all the cells present in the afterbirth are no longer oxygenated and may therefore spoil to some degree.
If the results of this examination are pronounced satisfactory, the placenta and annexes can be carried out of the delivery room into another area, in an appropriately sterile container. In the circumstances, medical staff participating in the management of labour, birth and afterbirth delivery are not involved in cord blood harvesting, which is significant in ethical terms[36].

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30 By centrifugation, red blood cells migrate to the lower part of the receptacle. The white blood cell and platelet layers settle as sediment above the red blood cell pellet. The plasma not containing cells constitutes the supernatant liquid. The procedure consists in eliminating the plasma by pipetting and then aspirating separately the layer of white blood cells, platelets and stem cells, while carefully not aspirating red blood cells. Some skill and technical expertise is required to obtain a satisfactory harvest of useful cells.

31 The English expression "buffy coat" is used by the scientific community internationally.

32 See the note in Annex 3 on mensenchymal stem cells and regenerative medicine.

33 At least two million cells with the CD 34 + marker per unit of UCB.

34 See note Annex 4.

35 If all the criteria for quality are satisfied, the harvested stem cells will be cryopreserved and registered to ensure traceability, in particular as regards the UCB unit. Then, after a lapse of time in quarantine to make sure that no transmissible infectious agents are present, the UCB unit will be entered into the registry for available bone marrow grafts, on the condition that quantitative criteria demanded by haematologists are met.

36 Later, conveyance of the placenta and annexes to the incineration site conforms to DASRI *déchets d'activité*

However, stem cells harvested in the above conditions, having spent a relatively long time without oxygenation, may have lost some of their viability, therapeutic properties or qualifications[37] for use in research.

It therefore seems clear, as was discussed above, that to collect cord blood while the placenta is still *in situ* has one major drawback: which is that it *could* detract from the close supervision required for mother and child in the immediate "post delivery" time period. Although it may be technically defensible, this is an activity which is added on to the existing workload of delivery room health carers[38]. Some professionals consider that it is unacceptable that a coincidence of objectives could be potentially detrimental to the health caring activity which is owed entirely to the birthing mother and her new-born child in the delivery room.
For this reason, CCNE considers that the extra work of harvesting cord blood, be it in private or public medical institutions, should not, for ethical reasons, be expected of the "existing workforce". Marketing surpluses generated by public allogeneic biobanks could be devoted to compensate for the increased payroll required to cope with this ethical necessity.

To sum up this second chapter:

- In the last ten years, it has become clear to an objective eye that there is a need for efficient public biobanks supplied by the harvesting of haematopoietic stem cells derived from cord blood. In accordance with the principle of abstaining from harm, it would be ethically appropriate to do everything possible to increase their number so as to reduce to an absolute minimum the need for donations of haematopoietic stem cells by healthy volunteers, although the indication, as reported by oncohaematological transplant physicians is nevertheless still entirely pertinent in a large number of cases.
- There is a growing need to increase, in allogeneic biobanks based on the principle of solidarity, the number of UCB units that can be used as substitutes for bone marrow grafts, exchangeable within a country and from one country to another. It can even be said that this is now a "burning obligation" for maternity departments and community biobanks.
- If cord blood harvesting continues — as is now the case — to be performed in delivery rooms, then the governing bodies of medical institutions must provide for extra human resources to staff licensed maternity units included in this public service project.
- In this event, the entire medical staff and the midwives operating in licensed maternity units must be given appropriate training to achieve optimal conditions for cord blood harvesting whenever the mother has consented to the procedure.
- Gynaecologists, obstetricians and midwives, without exception, must provide the mother with exhaustive information, as early in pregnancy as possible, on the therapeutic and scientific advantages that can be expected from not only cord blood harvesting, but also from the collection of other stem cells in the placenta and its annexes.
- The future mother's "informed" and written consent must be secured for any or all of the above sampling procedures.

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soignante à risque infectieux (medical waste involving a risk of infection) regulations.

37 In this respect, it may be worth noting that stem cells, haematopoietic ones in particular, are present in the adult body, in "niches" where the oxygen partial pressure is low, so that they are in a state of relative hypoxia which does not impair their properties or detract from their viability.

38 See Prof. Francis Puech's memorandum in Annex 5.

III - Types of banks for the conservation of products derived from cord blood, placental blood and from the cord lining

Biobanks are in the process of organising the storage of human biological samples and relevant personal data so as to ensure traceability. They inspire many hopes of medical advances, but there are a number of doubts and queries on how best to manage them in compliance with ethical considerations. For example, there may be a need to formulate policies governing economic interests or the potential commercial use of the research data derived from the study of cells the biobanks provided (including patents), or financing from private sources, or the issues of sample ownership and sharing[39].

In Opinion N°77[40] published in 2003 on "Ethical issues raised by collections of biological material and associated information data, CCNE was already considering that two different expressions might be used: biobanks and "biolibraries", or "biorepositories". Unlike "biorepository", "biobank" rather gives the impression that collections of human biological samples could become instruments involving economic power or transactions. It is worth noting that biobanks are an example of a particular kind of biological resource centre as defined by the Organisation for Economic Co-operation and Development (OECD) which provided them with Best Practice Guidelines in 2007.

In the context of a contribution to the public interest, the action of allowing biobanks to collect biological material may be viewed as a donation. That which is valid for cord blood should also be valid for products collected from the "afterbirth". The donation then becomes part of a general system of reciprocity insofar as the act of giving contributes to the common good.

A study conducted in France, Germany, Italy, Spain and the United Kingdom on awareness among pregnant women regarding cord blood stem cells and on their reactions to biobank storage options, revealed a notable preference[41] for banks based on principles of solidarity, a preference founded on common values such as benevolence and solidarity in connection with a pooling of the therapeutic outcomes[42].
The proliferation in the media of commercial marketing by cord blood biobanks underlines the importance of the role of obstetricians in raising awareness of women in early pregnancy by the provision of clear, loyal, scientifically proven and valid information on the choices open to them between the various kinds of biobanks: autologous, allogeneic and based on solidarity, allogeneic

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39 Onisto M, Ananian V, Caenazzo L. Biobanks between common good and private interest: the example of umbilical cord blood private biobanks. Recent Pat DNA Gene Seq. 2011 Aug 9 (online E pub ahead of print).

40 CCNE's Opinion N° 77 on "Ethical issues raised by collections of biological material and associated information data : "biobanks", "biolibraries", March 20, 2003.

41 The reactions of pregnant women would not therefore seem to be as such, an obstacle to a swift expansion of allogeneic biobanks in these European Union countries. The decision of the future mothers did not seem to be in correlation with income levels. As mentioned in research done by G. Katz quoted by Marie Thérèse Hermange in her report to the *Sénat* in 2008 (see note n° 8), 98% of women who were asked wanted the cord blood of their future child to be stored and put to use rather than being destroyed. Of the women, 75% had altruistic and public-spirited reasons for wanting such conservation to take place in public biobanks, while 23% preferred "mixed-use" banks where preservation served both their own family and the community, so as to be able to reserve for their children the potential benefit of stem cells derived from their own cord blood.

42 Katz G, Mills A, Garcia J, Hooper K, McGuckin C, Platz A, Rebulla P, Salvaterra E, Schmidt AH, Torrabadella M.Banking cord blood stem cells: attitude and knowledge of pregnant women in five European countries. Transfusion. 2011;51(3):578-86

and familial or mixed-use for both family and the community at large[43].

Privately owned and for-profit autologous cord blood banks are in a radically different category. From the start, their usefulness was not very clear in view of the low, or one could say infinitely small, autologous use of cord blood up to the present time. Because of procedural shortcomings and absence of consensus in the processing of cord blood by these privately-owned autologous biobanks, at this point and for the common good it would not be acceptable in all serenity to allow the use of their UCB units for bone marrow allografts: as a result, the cord blood which is collected in these circumstances is lost for everyone. CCNE therefore continues to hold the same opinion it expressed in 2002 and all the more so because the misleading and scientifically unfounded advertisements on the subject of this type of biobank have continued to incite future mothers to adopt attitudes which are based neither on logic nor on solidarity.
The possibility exists, nonetheless, that in branches of study still in the experimental stage today, autologous uses could emerge for regenerative therapies, either for neonates or to treat older patients. Should experimental results be validated by incontrovertible scientific publication, the statement that stem cell biobanks intended for autologous therapy purposes are not useful could be toned down.

The subject of new indications for haematopoietic stem cell transplants to treat highly debilitating congenital haemoglobinopathies such as thalassemia and sickle cell disease, is a very different matter. These haemopathies cause anaemia and numerous complications. Destruction of bone marrow at a young age and substitution with HLA-compatible UCB units obtained from a related but disease-free donor, can cure the haemopathy. As a result, banks of UCB units from a patient's siblings have now become reasonably desirable and are in fact desired by many haematologists.

These reasons militate in favour of a system with solidarity as its main priority. It would be the only way of ensuring a supply sufficient to cover the need for biological material to feed biobanks storing cord blood haematopoietic stem cells.
French regulations on the collection of products of the umbilical cords and the placenta, quoted by Madame Marie-Thérèse Hermange[44], show clearly that all necessary precautions are taken to ensure that UCB units stored in France are at the highest individual level of quality and volume, in contrast with other countries hosting cord blood biobanks. The French UCB units comply totally with the international consensus[45], which is a further strong motivation for increasing their numbers and diversity.

There is also a practical difficulty responsible for the scarcity of UCB units available for use in France: cord blood products are not banked because of technically deficient procedures. The information provided by Francis Puech when he was heard, showed that in a fair-sized public maternity unit, handling 5,500 deliveries per year, while mothers had expressed their decision and consent, for technical reasons — including the number of caesarian sections — cord blood could only be harvested in approximately 2,500 to 2,800 cases, i.e. almost half the number of births. Furthermore, in only 30% of cases are volumes collected sufficient to produce UCB units in competent laboratories. Finally, only 10% of the harvested units possess all the characteristics required to turn them into UCB

43 And yet, to quote Nico Forraz, the number of public allogeneic biobanks seems to be approximately 56,000 worldwide (of which less than ten in France), while there are far greater numbers of private banks for purely autologous purposes or for mixed use.

44 Report n°79 to the *Sénat* on November 4, 2008 on "the therapeutic potential of stem cells extracted from cord blood", p.25-26

45 World Marrow Donors Association (WMDA) Combined Private and Public Banking of Cord Blood and other related products.

units. As a result, only five to ten per cent of deliveries in a licensed maternity unit can be expected to yield a registered UCB unit for collective use (in other words, 275-350 UCB units per year in the case quoted above). A minimum of 60 licensed maternity units of this same size, working in coordination with a recognised biobank, would be needed to achieve an objective of around 20,000 UCB units harvested per year, which would make it possible to obtain in the middle term, as is desirable and desired by specialists, a stable stock of over 50,000 UCBs covering most of the HLA phenotypes required for bone marrow grafting in France.

There is another problem which prevents hospitals with maternity wards from being enthusiastic about the development of these biobanks: under current regulations, the lump sum payment to institutions with a licensed maternity ward is €90 per sample, whereas the cost incurred in time spent and various consumables is approximately €200, not taking into account the payroll increases due to extra staff in the delivery room for health safety reasons[46].

At a later stage, the full procedure leading to the registration and biobanking of UCB units adds up to the cost of around €2,000 per transplant. The price of sale of UCB units in France is approximately €8,300 including the cost of storage[47]. When the units are sold abroad to foreign transplantation centres, they are priced at €14,500. By way of comparison, the corresponding price paid when units are imported, is of the order of $25,000 and sometimes more, as much as over $45,000.

To sum up this third chapter:

- There is no more reason in 2012 than there was in 2002 for considering that privately-owned for-profit biobanks, set up for the conservation of UCB units to be used exclusively as substitution for autologous bone marrow, with the single indication of possible marrow self-grafting, should be authorised and developed. The overwhelming majority of future mothers interviewed had no wish for this to be done. Examples of advertising for other uses of autologous stem cell harvesting, unsupported as it is by any scientific evidence, reinforces CCNE's position on this matter.
- Autologous uses for purposes which may still be experimental but are already reasonably promising in regenerative indications, either immediately after birth or later in life, would however justify qualifying the statement that biobanks for autologous uses are totally futile. All the UCB units stored, regardless of the kind of biobank concerned and of its financial status, **must conform to the same international standards as regards harvesting, procedures, quality and volume.**
- The indication for using two or even three UCB units from donors purportedly HLA-identical, for adult bone marrow grafts, has now become a perfectly credible possibility and already in use by certain oncohaematological teams.
- For the target figure of 50,000 registered, available and unassailable-quality UCB units to be reached in the near future for use as allografts of haematopoietic stem cells in France and abroad, the number of licensed maternity departments in France must be increased to sixty[48] at the very least.
- From 2002 onwards, new indications for intra-familial allografts of haematopoietic bone

46 See Annex 5 for an evaluation of the number of extra workers required for the safe servicing of licensed maternity units.

47 The price is set at a very high level compared to production costs in order to finance the development of French maternity departments and banks.

48 As of end March 2012, there are ten functional UCB units biobanks in France, in association with sixty public or privately-owned maternity units responsible for 130,000 births per annum. The stock of validated and available UCB units totals approximately 16,500, which is twice as much as two years ago.

marrow were discovered, i.e. certain congenital genetically transmitted haemoglobinopathies, so that there is a current of opinion suggesting that allogeneic "familial[49]" biobanks should be created.

- These familial biobanks must not be exclusively private in view, in particular, of the usually low income of most of the people concerned by these cases (ethical principles of justice and solidarity).
- The case of familial biobanks for allogeneic uses deserves to be considered and dealt with separately and, by definition, to be clearly set apart from that of biobanks for solely autologous purposes. It should be possible for the cost of running these familial biobanks to be borne, at least in part, by public funding.
- For the sake of efficiency and solidarity, (when none of the siblings has inherited the threatened congenital haemopathy and the UCB units will not be needed), these familial biobanks should become available for allografting outside the family.

IV - Collection, use and possible storage of mesenchymal — or even endothelial — stem cells derived from the cord and the placenta

Recent data on the therapeutic potential of mesenchymal stem cells present in the placenta and in the middle part of the cord lining strongly suggest that fundamental research on these cells should be continued in parallel with preclinical, followed by clinical, research. In a different form, this is again raising the question of whether powerful technical platforms[50] should be developed for the processing of placental and cord-derived cell products, preferably once the afterbirth has emerged and has been checked to be sure it is complete.
Among the potential therapeutic uses of mesenchymal stem cells from this source, their anti-inflammatory properties and their capacity to prevent graft-versus-host-disease (GVHD) stand out particularly, so that they can serve a useful purpose in bone marrow grafting. As a consequence, HLA phenotyping[51] is required before they are biobanked.

These varieties of stem cells derived from the "afterbirth" before it is destroyed can be collected independently from, or consecutively to, the harvesting of cord blood. If the afterbirth is to be harvested, it must first be transported in a sterile container into another area, apart from the delivery room, and the procedure performed by specially dedicated staff, not members of the maternity ward's medical team. Traceability and HLA phenotyping of mesenchymal stem cells obtained from the same cord as a UCB unit could be of particular importance for later use, such as treatment for graft rejection or GVHD in the event of bone marrow grafting. This may also be the case of regenerative treatment for the same beneficiary.

Objectively, cord blood harvesting is equivalent to a donation and therefore requires maternal consent. Ethically, the issue arises of whether specific consent from the mother is required for the harvesting of stem cells which can be obtained by the processing of "*res derelictae*". CCNE draws attention to the fact that since such action is harmless, pertinent, benevolent and equitable, these characteristics would tend to converge in favour of consent being given. For this reason, the

49 See Annex 2 for biobank definitions.

50 Such technical platforms, whose status would need to be defined, i.e. public, private, not-for-profit, or even private but with regulated pricing systems, would be shared by research teams, or even practitioner teams involved in their use for clinical research. They would have to be completely separate from biobanks storing UCB units.

51 They could also enhance the engraftment process by supplying the stromal cells which are essential for the differentiation of haematopoietic stem cells once they have arrived in the bone marrow "niches".

Committee considers that a simple absence of refusal on the part of the mother would also be acceptable. Consent (by non rejection) could be asked for by medical practitioners in charge of clinically supervising the pregnancy, when they ask for consent to the donation of cord blood.

In the view of most authors, mesenchymal stem cells, derived from the peripheral part of the cord, or even from placental annexes, are technically easy to harvest and culture once the afterbirth has arrived. They can be easily harvested in the delivery room. They are characterised as a heterogeneous package of cells, as are mesenchymal stem cells from bone marrow or fatty tissue, or even from cord blood[52].

Organisations in charge of harvesting and processing these stem cells could store them in collective access biobanks so that mesenchymal stem cells could be used for the treatment of patients whose haematopoietic stem cell grafts for onco-haematological disorders have gone amiss.
These organisations could also offer the products of their harvesting through specific "biorepositories" for research, mainly fundamental and preclinical.

On two occasions in 2010[53], the French *Académie de Médecine* published unanimously agreed and seriously documented opinions on the subject of expectations arising out of the therapeutic potential of mesenchymal stem cells in general, but more particularly those derived from the placenta and Wharton's jelly. The additional potential from endothelial stem cells also derived from the cord lining, however, has not so far been the subject of many published trials.

Mesenchymal cells[54] in general are also the subject of a large number of publications. Specific stem cells derived from placental products and the cord deserve a further examination of ethical issues arising out of the use of these "afterbirth" components.

The work done by Prof. Zong-Chao Han's team[55], quoted by Jacques Caen in his report to the *Académie de Médecine* seems to suggest that it is possible to collect a large number of mesenchymal stem cells in the cord and placenta periphery. With appropriate culture, these cells can provide stable lines (this terminology is disputed by some haematologists), which does not seem to be the case for mesenchymal or endothelial cells derived from cord blood itself, or even mesenchymal mesangial cells derived from adult adipose tissue or bone marrow.

These facts are of scientific significance insofar as they have been reproduced by other research teams, in particular in France in the *Institut de recherche en sureté nucléaire* (IRSN – Institute for

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52 These cells:
- are immature,
- have a high proliferative potential and are generally multi- or even pluripotent, with a potential for giving rise by culture to stable cell lines,
- capable of identical self-renewal, or renewal to asymmetric mitoses, producing one half of identical cells for all their properties, and another half of cells capable of evolving to tissular differentiation,
- flexible by essence, that is capable of becoming quiescent in the event of hypoxia or, on the contrary, of multiplying depending on yet to be defined environmental tissular circumstances,
- have low immunogenicity and are endowed with anti-inflammatory properties.

53 a) Cord-derived and Placental Stem Cells: from Research to Therapeutic Application. (*Les cellules souches du cordon et du placenta : de la recherche aux applications thérapeutiques*) Report 10-1.J.Caen. Bull Acad Nale Méd 2010, 194, N°1, 141-152 b) Stem Cells and Therapeutic Perspectives, (*Cellules souches et perspectives thérapeutiques).* Report 10-12. J.Y. Legall and R. Ardaillou Bull Acad Nale Méd 2010, 194, N°8, 1601-1620.

54 See Bruno Péault's editorial on this subject and related articles in issue n°12, volume 26 of *Médecine Sciences* December 2010.

55 J. Caen. Bull Acad Nale Méd 2010, 194, N°1, 141-152.

Radiological Protection and Nuclear Safety) in cooperation with the research centre of the Percy hospital or in Lyons par Dr. Nico Forraz's team in the Lyons-Saint Priest Institute for Cell Therapy.

Compliance with approved procedure and the processing of cell samples collected in licensed maternity wards should be possible with the help of a restricted number of dedicated and adequately equipped technical platforms[56]. It should be possible for them to be shared by several teams and supply public biobanks with mesenchymal stem cell lines whilst ensuring the traceability and the quality of the cell samples so that they could be entered into appropriate registers.
Other samples could be harvested by research teams and registered in biorepositories, exclusively for research purposes financed specifically out of official research and development funds (*BCRD - Budget civil de recherche et développement*).

Available scientific publications on the properties of mesenchymal cord and placenta-derived stem cells are, in some cases, indisputably credible. This is also true for some which are published in the field of regenerative medicine — medicine for "repairing" the body — relating to short series of patients so far which implies that work that has already received a degree of confirmation should be pursued[57]. As yet, they are insufficient in number. Some of them do not present a sufficient sum of reproducibility criteria for their results to be considered as definite as are those which concern cord blood-derived stem cells; they cannot therefore be moved on from the clinical research stage to fully fledged therapeutic practice. However, in the light of already established facts, harvesting non haematopoietic stem cells from the products of the cord lining and other placental structures could become more systematic in view of their potential, if not as yet current, importance for fundamental and applied research.

Cord and placenta-derived mesenchymal stem cells have the advantage of being young, multipotent at the minimum, and probably even pluripotent. Their potential is at least comparable to that of iPSCs (induced pluripotent stem cells) obtained through genetic modification of mesenchymal cells collected from adult fatty tissue. Their advantage over iPS cells is that they are young, and above all, immuno-naive, that is that they have not yet been "compromised" by their environment[58], which provides them with a specific status within the stem cell community.

In the short or medium term, these cord and placenta-derived mesenchymal stem cells could, depending on the results of ongoing applied research,

- be used by pharmacologists for screening potential medications on cells of human origin,
- be used for regenerative medicine in autologous grafts, but also in HLA compatible allogeneic situations.

Their use, possibly autologous, as that of autologous cord blood, currently the subject of experimental work for regenerative medical purposes, could warrant a reversal of the prohibition of exclusively private and autologous biobanks, providing the scientific data is supported by evidence.
It is true that the administration of autologous cord blood has proved to be effective to some extent in the prevention or repair of disability in cerebral palsy. Since *in utero* ultrasonography can be used to diagnose cleft palates, collecting placenta blood and stem cells could be programmed before birth and surgical repair of this congenital defect could be considerably improved by simultaneous administration of the child's own cord blood; such procedures are, to be sure, still experimental, but

56 A possibility would be for these technical platforms to invoice their services at cost price, including depreciation, maintenance, consumables and equitable return on capital, under strict official supervision if the platforms were to have private status.

57 See Forraz N, McGuckin CP. The umbilical cord: a rich and ethical stem cell source to advance regenerative medicine. Cell Prolif. 2011 Apr;44 (Suppl 1):60-9, for references to these publications.

58 Nico Forraz during the hearing in CCNE's Technical Section on April 15th 2010.

they do seem to be already quite promising for such indications.

To sum up this fourth chapter:

- The potential, in terms of research, of mesenchymal cord lining and placenta derived stem cells, is now corroborated by a large number of scientific studies.
- In future, harvesting stem cells from the cord lining should become more systematic.
- Mesenchymal cord lining and placenta derived stem cells are plentiful, can be cultured and their number amplified efficaciously. It may even be possible to obtain stable cell lines.
- The need for stem cells for pharmacological screening could be satisfied by the use of such stable cell lines.
- The hopes born of their use in regenerative therapy, both neonatally and later in life, are sufficient in themselves to warrant research supported by scientific and technical agencies and public establishments for biomedical research (EPST - Etablissements publics à caractère scientifique et technique).

V - Conclusions:

Through the post-natal harvesting and processing of cord blood, following internationally recognised rules, it is possible to obtain haematopoietic stem cell units constituting excellent grafts as a substitute for bone marrow collected under general anaesthesia from healthy volunteers.
The number of indications, as well as the successful engraftments obtained with cord blood-derived haematopoietic stem cells as a substitute for haematopoietic bone marrow, have increased in the last ten years. That is good reason, together with their success rate, to consider them **evidently beneficial**. The number of UCB units available in France is not a good match for the growing needs of onco-haematological medical teams working with haematopoietic stem cell grafts to alleviate medullary aplasia induced by the management of leukaemia.
By reason of **solidarity**, therefore, (be it national or international), promoting the post natal harvesting and processing of cord blood is recommendable. Such harvesting has no known direct ill-effects, but does make it necessary to ensure that the procedure does not distract medical teams in maternity wards from their task of providing health care for mother and child.
The diversity of histocompatibility phenotypes, both in donors and recipients, militates in favour of having available a very high number and very great diversity of haematopoietic stem cells for grafting, which is difficult to achieve for one country alone. International solidarity, from which France benefits as regards available grafts, is a further argument in favour of increasing the number of validated and registered units in French biobanks.

In view of the low yield of cord blood harvesting actually leading to registration in a biobank that can be expected from the annual number of births in licensed maternity wards, harvesting should be extended to a much larger number of births and to a population as diversified as possible. If future mothers are informed precisely and exhaustively as soon as possible during the pregnancy monitoring process on the therapeutic and scientific possibilities offered by the harvesting of cord blood and other stem cells collected from the afterbirth, there should be no prejudice to future mothers' independence of decision and their **informed consent to an act of fairness and solidarity** should be facilitated.

Placenta blood autografts as a substitute for bone marrow are still at this time only suitable for indications so rare as to be almost inexistent, and therefore sufficiently exceptional to cancel out the

justification for biobanks created for that sole purpose. Their private for-profit status leads them, all too frequently, to publishing advertisements which have no confirmed scientific basis and are therefore often deceitful.

Research on mesenchymal stem cells derived from cord blood, the cord itself and the placenta should be encouraged. Stem cells are abundant in the cord and placenta and harvesting them presents no difficulties.

The potential of mesenchymal stem cells, both for fundamental and applied research, is now corroborated by the international scientific community.

In view of the substantial hopes raised by various autologous and allogeneic regenerative therapy trials, efforts should be made to develop research — too sporadic so far — on the properties of these particular easily accessed stem cells derived from tissues which would otherwise inevitably be incinerated as waste.

In these circumstances, CCNE considers that it would be ethical to:

- **Promote** an extensive campaign to inform pregnant women of the possibility of donating cord and placenta products at birth and of the usefulness of the procedure, to ask them for their consent well in advance of delivery, that is during pregnancy monitoring. Give priority to the principle of donating to solidarity-based biobanks or for research.
- **Disseminate** information to all medical and non medical carers participating in obstetrical and gynaecological activities on the possibility and usefulness of cord and placenta product donation at birth.
- **Expand** the number of maternity units licensed to harvest cellular products derived from cord blood, from the cord itself and from the placenta. Finance at their real cost, using surpluses generated by public biobanks, expenses for the purchase of consumables and for payroll increases incurred by the maternity units participating in the harvesting procedures. Augment the human resources in the delivery rooms of these units so as to avoid any risk of deterioration of the quality of healthcare to birthing mothers and neonates involved in the procedure.
- **Concentrate** the processing and conditioning technical platforms for these cellular products complying with international standards. Have their transfer prices verified by independent public bodies.
- **Require** from all biobanks involved with cord and placenta products, irrespective of destination and organisation, that they apply fully the quality and volume criteria demanded by consensual international standards for potential allogeneic grafting.
- **Promote** the development of familial biobanks based on principles of solidarity by encouraging the harvesting of cellular products derived from cord blood, the cord itself and the placenta in families whose children are exposed to the risk of genetically inherited congenital haemopathies.
- **Urge** public bodies in possession of the required information to publish cost comparisons of the various medical options for the treatment of congenital malignant haematological pathologies: bone marrow graft using haematopoietic stem cells donated by a healthy volunteer or using cells derived from cord blood, or no graft.
- **Encourage** research institutions to call for fundamental research projects on all the kinds of stem cells, be they derived from cord blood or from the cord lining or the placenta; to develop public financing for fundamental and applied research on the cellular products derived from cord blood, the cord itself and the placenta. In parallel, suggest they stimulate

applied research, clinical in particular, on the use of various kinds of stem cells derived from the cord as a whole so as to foster, for example, neonatal treatment of cerebral ischemia and cleft palate.

Paris, February 23rd 2012

Annex 1

Some of the properties of stem cells, in particular those found in cord blood, in the cord lining and in the placenta itself.

The existence of "stem" cells, as they were called, which was suspected ever since the 1950s, was evidenced in 1980[59], in mice and 17 years later in humans. Stem cells have two distinctive properties: they differentiate into specialised cell types and they are capable of very numerous self-renewals. These cells play a role in embryogenesis and in the maintenance of the adult body (tissue renewal and regeneration). This signifies that they must be present in the body throughout life, although their proportions are smaller in adult tissue than in embryonic or foetal tissue.
The very first stem cell is formed when the sperm cell enters the ovum through natural fertilization or *in vitro*. When it goes through its first cell division, it produces two stem cells which are "totipotent", meaning that they can differentiate into all embryonic tissues as well as into embryonic annexes (the placenta, for example), so that each one of them is capable of producing all by itself an embryo which will become an entire foetus if it reaches a stage where it can be implanted into the uterus. After a certain stage of development (the "blastula"), stem cells are no longer totipotent and are henceforth "*pluripotent*", meaning that they can differentiate into cells of any of the body's tissues (including germ cells), but can no longer by themselves give birth to an entire embryo. At this point, reproductive cloning therefore ceases to be possible without hypothetical and additional manipulation to enable them to regain their totipotency. As for "*multipotent*" stem cells, they can only differentiate into cells derived from the same primary germ layer[60]. They are some of the stem cells present in the adult body, which also contains "unipotent" stem cells, i.e. cells still further down in the differentiation process, so that they can produce only one cell type.
Apart from their potential for differentiation into various types of tissues and adult cells, the fundamental property of stem cells is self-renewal[61]. The properties of stem cells depend on their origins and on their replicating potential, that is the number of divisions they may give rise to, both *in vitro* and *in vivo*, without the benefit of any "age" dependent processing (and so this is not the case for the induced pluripotent or iPS cells). Therefore, pluripotent stem cells after the blastula stage have a greater potential than that of adult stem cells.

At birth, whereas most of the organs are completely differentiated, there are still some quiescent stem cells to be found located inside certain organs; some of them are in the blood circulating in the foetus or in the blood circulating to and from the placenta.
These are the circulating stem cells which are harvested in the umbilical cord blood vessels, the international acronym of which is UCB ("Umbilical Cord Blood". In this blood are stem cells from the three germ layers but in vastly different proportions, mainly the haematopoietic stem cells capable of producing, in a favourable biological environment, all the cell lines in the composition of adult blood.
In the adult, in most, if not all the body tissues, there are very small quantities of stem cells belonging to the same tissues' cell lines. For example, fat belonging to tissues derived from the mesoderm are

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59 Evans MJ,Kaufman MH. Establishment in culture of pluripotential cells from mouse embryo. Nature. 1980 ; 292 :154-6

60 During embryogenesis, cells begin to specialise into three "germ layers", the outer layer being the ectoderm giving rise to the skin and the nervous system; the middle layer being the "mesoderm", from which for instance, muscles, the skeleton and blood vessels develop; finally there is the "endoderm" which will be the origin, mainly, of the gastrointestinal tract.

61 When a stem cell divides, one of the two daughter cells is always entirely identical to the cell that gave birth to it. The other one differentiates to tissues being formed.

part of the mesenchyme and fat-derived stem cells are called “mesenchymal” stem cells.
In the middle part of the umbilical cord lining, called “Wharton’s jelly”, which comes from the mesoderm, there are a great number of mesenchymal stem cells whose properties are such that they could be significantly effective in “repair” cellular therapy.

Annex 2

Biobanks and preservation of cord blood and of stem cells derived from the cord lining and the placenta.

In 2003, CCNE published an Opinion (n° 77) on the Ethical issues raised by collections of biological material and associated information data. The German National Ethics Council (Nationaler Ethikrat), concurred with CCNE in underlining that collecting biological samples, human samples in particular, raised a great number of ethical and legal challenges. They insisted on the need for a coherent regulation framework, at both national and international levels. Both Ethics Committees granted pride of place to the issue of the donor's informed consent and emphasised that storage is not the equivalent of acquisition or appropriation of the items collected and their relevant personal data.
The term "biobank" [62] seems to imply that collections of human biological samples, in particular the larger collections, are to become instruments of economic transactions or power. CCNE remarked, that from a symbolic viewpoint, it might have been preferable to coin an expression such as "bio-libraries" to describe this type of biological resource centre (BRC), as defined in 2007 by the Organisation for Economic Co-operation and Development (OECD) in their Best Practice Guidelines. CCNE underlined the role of a storage structure embedded in a network of rights and duties which must be regulated and defined in identical terms, be they public or private entities.

The World Marrow Donors Association (WMDA) [63] defined international consensual quality criteria for the collection, storage and use of cells derived at birth from cord blood. The criteria include the general organisation of the registry, donor recruitment and characteristics, data collection techniques and management, the harvesting, processing and transport of haematopoietic stem cells, monitoring of both recipient and donor, financial considerations, etc.
The founding principle is that cells harvested from cord blood at birth, be they collected for the use of the family or for altruistically allogeneic purposes, should in every case be stored in appropriately organised biobanks, clearly separated to match the wishes expressed by the family requesting that the cord blood be collected, and subject to all the good practices procedures demanded for public biobank accreditation.

The potential uses for biobanks storing cord blood and stem cells derived from the cord lining can be:

- **Autologous**: storing the cord blood for the same new-born's own use. The hypothetical probability of this blood being used as a substitute for autologous haematopoietic bone marrow is infinitesimal. *These biobanks do not make it mandatory to observe fully international standards, in particular HLA phenotyping.* UCB units stored in these banks cannot be registered for exchanges. These were the reasons for CCNE's censure expressed in 2002 in its Opinion n° 74. These biobanks, referred to as autologous, in their vast majority are privately financed. None of them are French, although they are neither prohibited nor authorised in France. Nevertheless, they represent the majority of biobanks for UCB units existing worldwide (currently more than a million).

- **Familial**: for this purpose, in a family where there is a risk of congenital haemopathies, the cord blood of all the siblings is collected systematically. The disease is only expressed if it is transmitted simultaneously by both parents, in which case the status is referred to as 'homozygous carrier of the two chromosomes responsible for the pathology'. Statistically, one quarter of the siblings are, unfortunately for the individuals concerned, homozygous. Another

62 For more information: F. Bellivier, C. Noiville « Que sais-je ». PUF, Paris, 2009 pp. 114 to 122

63 http ://www.worldmarrow.org

quarter inherits no chromosome capable of transmitting the condition, so they are neither sick nor are they healthy carriers. The remaining half of the siblings are like their parents, that is healthy heterozygous carriers. As a result, in one family of siblings, three quarters of the children are disease-free or healthy carriers whose haematopoietic stem cells may be able to cure a sick sibling through a graft.

- The young brothers and sisters of a sick child are therefore potential "donors" of their cord blood haematopoietic stem cells for an allogeneic marrow graft performed once the sick child's own abnormal bone marrow has been destroyed. This is the case, for instance, of drepanocytosis (sickle-cell disease) [64], a very debilitating condition, generating a great deal of suffering and entailing expensive care throughout the patient's life. In this set of circumstances, there is undoubtedly justification for familial use of the cord blood and, if the parents wish use to be exclusive, the cord blood units will not be available for listing in national or international allograft exchange registries. Depending on the prevailing national health care policy, they could be stored in public biobanks operating as an expression of the community's solidarity with children affected by this homozygous haemopathy. If no such policy is in force, the families concerned might well decide to insure themselves against the risk of disease and pay a private organisation for harvesting and storing the allografts, for the exclusive use of their own children in the event that they inherit the disease.

- **Allogeneic for solidarity**: in this type of use, all the harvested cord blood units would, after the mother has given explicit consent, be processed according to international "standards" and selected in the light of criteria for quality and quantity so that they could be listed on national and international exchange registries. Mainly, such biobanks are publicly financed; there are some 56,000 of them worldwide. There are also some private not-for-profit biobanks, most of them created and run by foundations.

- **Allogeneic, Familial, for Solidarity**: this use defines a biobank where it is mandatory that international standards govern the harvesting and processing of transplants:

(i) in part used exclusively for purposes founded on **solidarity**, allowing allografts for patients unrelated to the family concerned. The blood units that can be used for grafting are listed on national and international exchange registries;

(ii) in part used for the **family**, as described above. During an initial period of time, the units are stored for priority use by siblings. *But in the event that none of the siblings are homozygotes, or if the homozygote has already undergone treatment and some leftover blood units are available for transplant, the preserved units can be donated to the community.* **The possibility of allogeneic donation based on solidarity must be subject to the mother's informed and written consent before proceeding with harvesting and banking;**

(iii) Once specific use has been defined, the donated UCB units are listed on the transplant exchange registry. The biobank thereby acquires "**familial and for solidarity**" status.

The financial status of such banks may be exclusively public, but possibly joint private and public ownership.

It appears clearly that the autologous, familial-and-allogeneic or allogeneic-for-solidarity nature of

64 http://www.inserm.fr/thématiques/genetique-genomique-et-bioinformatique/dossiers-d-information/drepanocytose

the harvesting and preservation processe is defined and analysed as a function of intended use.
The matter of public or private financing for investing in a biobank and the running costs is a discussion on another level.

In the event that the harvested cord blood is of the required quality but insufficient in quantity to be classified as a suitable UCB unit for transplant substitution purposes, it could arguably be preserved for autologous use in regenerative therapy, but this is a possibility which is not, as yet, supported by confirmed scientific facts. Above all, it should be possible to sell it at its true cost price for the purpose of research, irrespective of the financial status, be it private or public, of the medical team responsible for harvesting.

Annex 3

Regenerative medicine, cell therapy and mesenchymal stem cells.

Regenerative medicine is the term used to designate the process of replacing or regenerating injured organs, tissues and cells so that they may regain what are deemed to be normal functions. Incidentally, it is expected of this group of techniques that they could gradually make up the shortfall in organs available for transplant. The expression "regenerative medicine" seems to have been coined in 1992 by Leland Kaiser in an article on hospital administration[65] in which he considers the possibility of changing the outcome of chronic diseases by regenerating failing or dysfunctional organs. With this concept in mind, scientists worldwide are attempting to develop cell substitution therapy strategies.

They have therefore been working on the use of stem cells, mesenchymal stem cells (MSCs) in particular, putting to good use their self-renewal and differentiation properties. For example, MSCs are isolated from mononuclear cells in bone marrow and adipose (fatty) tissue, but also from a part of the umbilical cord called "Wharton's jelly", originating in the mesoderm. MSCs give birth to the connective tissues of the skeleton (bones, cartilage, adipocytes, etc.). They may also be able to differentiate into other cell types, such as skeletal, cardiac and endothelial cells, or even cells from other embryonic origins. Their highly multipotent characteristics and their immunomodulatory capacities qualify them as promising candidates for regenerative cellular therapy.

The importance and potential of MSCs in this respect is illustrated by the fact that, in the last ten years, the National Library of Medicine of the National Institute of Health of the United States[66] contains references to over 6,000 international scientific publications responding to the key words "regenerative medicine and stem cells". Almost a quarter of these articles relate to MSCs.

In vivo, MSCs play a regulatory and supportive role for haematopoiesis (creation of the "niche" where haematopoietic stem cells reside, production of interleukins and growth factors). As a result, clinically they can provide haematopoietic stem cells with the potential for engraftment either in bone marrow or in cord blood. They also participate in the attenuation of acute graft *versus* host disease, (aGVHD) after allogeneic transplantation. But clinically, the value of MSCs is not limited to "marrow" transplants or their haematological applications. Currently they are under study (sometimes even under clinical study) for potential therapeutic applications in tissue repair: bone regeneration, revascularization (limb ischemia), joint repair, myopathies, myocardial infarction, heart failure, micro-environmental repair, immunomodulation and even neurodegenerative diseases.

In Germany, for example, scientists working in the Mesentech group are trying to develop regenerative therapy for age-related macular degeneration (AMD), using *in situ* retinal implants of MSCs derived from the patient's own fatty tissue.

65 Kaiser LR. The future of multihospital system. Topics on health care financing 1992;18 : 32-45

66 US National Library of Medicine of the National Institute of Health (Pubmed).

Annex 4

The histocompatibility system and its role in organ or tissue transplantation.

During the previous century, in the 60s, Jean Dausset demonstrated first in a murine and later in a human model, targeting women who had many children, that mothers tend be immunised by their pregnancies against antigenic components originating from the father. The model used skin grafts because engraftment or rejection are immediately visible. Skin grafts between mother and father and *vice versa*, and between mother and children and *vice versa*, showed both for murine species and humans, that graft rejection took place significantly more quickly when the grafts were from father-to-mother or children-to-mother than the other way around.
He found that the mother rejected the father's skin more quickly than the children's. He therefore inferred that the immune system was involved in skin grafts and that pregnancy immunised the mother against the father's antigens.
He later demonstrated that specific individual antigens existed not only on the surface of all of a person's leucocytes and platelets but also in their tissues and organs, the skin in particular, and on the surface of germ cells. He was awarded the Nobel Prize for these discoveries.
Jean Dausset and his fellow workers came to the conclusion that there must be a human histocompatibility system, and their subsequent contribution to classifying it into groups was substantial. There is very little likelihood that any chance selection of two individuals will be carrying the same antigens. Internationally there was agreement on referring to the human leucocyte and platelet antigen phenotype as the HLA phenotype[67].

These histocompatibility antigens are capable of provoking in another human the production of antibodies directed against them. The antibodies are primarily responsible for graft rejection following organ transplantation. Pregnancy itself is a semi incompatible allograft since the foetus carries a complement of specific leucocyte and platelet antigens, half of which are the mother's and the other half, the father's, so that the antibodies which are isolated from the mother's plasma are capable of destroying the father's lymphocytes[68] and, to a lesser degree, some of his children's lymphocytes.

Whatever kind of transplant is being considered, in particular grafts of haematopoietic stem cells (bone marrow or cord blood grafting), HLA typing verifies compatibility between donor and recipient and therefore facilitates the ultimate success of engraftment.

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67 HLA is the acronym for "Human Leucocyte Antigens".

68 Lymphocyte destruction is evidenced by the fact that a dying lymphocyte easily integrates certain dyes while a live cell does not. If plasma (containing specific antibodies to the antigens carried by the lymphocytes) is put in contact with the father's lymphocytes, it is possible to "see" the cytotoxicity contained in the mother's plasma.

Annex 5

Factors for the evaluation of the increased number of midwives to be recruited as a consequence of licensing maternity departments to collect cord blood:

This evaluation refers to the Besançon University Hospital's maternity ward, the first to be licensed in France for the collection of cord blood.
The evaluation is based on the one hand, on the time required for information and sampling procedures and, on the other hand, on professional midwife reference times for harvesting placenta blood on the ward as required for coordinating and performing this task on a daily basis.

To be exhaustive, all the activities either directly related to sampling or indirectly connected to the procedure such as the training of new recruits, logistics, management of paper work, etc., must be accounted for.

- For **one sampling**, times pre-, per- and post-natal, can be identified as follows:

	Average time per unit in minutes
Initial information collected during pre-natal follow-up, securing consent	**20 - 30**
Final check of absence of contraindications in delivery room, sampling and traceability	**35**
Post-natal information to mother if collection bag is non standard	**5**
Post-natal medical interview if collection bag is standard	**40**
Neonatal clinical qualification/paediatrician if bag is standard	**10**
Total	**120 minutes per unit collected**

In addition:

- Daily logistics and coordination with the *Etablissement français du sang* (EFS - French Blood Agency) for despatching the bags = **on average 13 minutes per day**)
- Training and supervision of new sampler trainees, i.e.:
    - Individual or collective (as the case may be) introduction to procedures, documents pertinent to placenta blood donation together with information regarding good practices
    - Supervision and evaluation of two information sessions on placenta blood donation and provision of consent documents
    - Supervision and evaluation of five placenta blood collections and sampling of maternal blood test tubes
    - Supervision and evaluation of two post-natal medical interviews

A total of: **460 minutes** for complete training of **sampler (#7.7 hours). Normally, all midwives should be capable of collecting placenta blood 24/24.**

Since all those who have not worked in the delivery room for over six months must re-qualify for sampling upon their return by means of a refresher course, updating theory and practice, a further

two collection sessions under supervision are required **(75 minutes of the trainer midwife's time, to be added to initial training time).**

- Management of documentation and traceability of good practice validation: **1.5 to 2 hours per month**
- Participation in annual EFS meetings (Bank Medical and Technical Committee): **2 to 4 hours per year, once the system is well-rehearsed (much more frequent at first)**

- Briefings and refresher courses for all members of the team, hospital students and other staff (general practitioners, etc.): **time required varies depending on unit dynamics and commitment to developing the activity and promote quality sampling.**

It may be necessary to spend time post-natally on telephone follow-up and reminders in the event of difficulty in obtaining data for bag security (during the quarantine required to verify the absence of any transmissible infectious agents in collected blood and mother's blood).

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Translating this evaluation into new requirements for full time employment equivalents for health carers in maternity units licensed for the harvesting of cord blood

For 2750 births per year followed by sampling, the minimum midwife time needed, on the basis of two hours per unit collected, would be 5500 hours per year to which must be added time required for initial training and refresher ongoing training courses, that is 24 hours per year and per midwife working in the maternity unit. Taking as an average work time 205 days per year, including ward duty, that is approximately 1750 hours per year, this means adding a minimum of four full time midwife equivalents for this maternity department which performs 5500 deliveries per year and is able to harvest 275 to 300 UCB units per full active year.