National Consultative Ethics Committee for Health and Life Sciences

Opinion n° 93

Commercialisation of human stem cells and other cell lines

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Professor Degos referred to the National Consultative Ethics Committee on problems arising from the commercialisation of therapeutic cells and, more generally, the products of cell therapy or of cellular and tissular bioengineering. To respond fully to the referral the Committee decided also to consider matters arising out of the possibility of commercialising human stem cells, obtained, processed or even modified by recent biological technology. This Opinion deals with the ethical difficulties which arise or could arise out of the possible commercialisation of human stem cells, both non-embryonic and embryonic, and of other cell lines[1]. It also broaches a number of issues which are directly connected to such difficulties: the commercialisation of products of the human body, the relationship between ethics and the market and the various forms in which financial value becomes pertinent, from the time when a stem cell is harvested until it is put to therapeutic use, for the benefit of an identified or indeterminate patient.

The following reflections and recommendations bear on a subject for which developments could be both rapid and unexpected so that it is difficult to lay down hard and fast rules once and for all.

Research on stem cells, both embryonic and non-embryonic, has developed considerably in the last decade. For many diseases, regenerative medicine based on the use of stem cells is a reasonable therapeutic prospect. Patients, physicians and scientists are considering any advances in this field with the closest attention. Numerous research centres and pharmaceutical companies have already invested considerable financial resources in the sector. Potential investors generally wish to be certain that inventions will benefit from legal protection in the form of a patent and that they will be able commercialise them. This entry of trade in the field of research and medicine bearing on an entity, the cell, which is indisputably an element of the human body, raises ethical problems regarding the nature of the elements or products which would be the subject of possible commercial transactions: up to what stage is a stem cell an element of the human body in the strict sense of the meaning? Do the processes it must undergo to preserve or put it to use change its status so that it becomes a therapeutic product?

Elements or products of the human body are generally considered in a number of countries as being protected from any form of commercialisation. The possible patentability of genes has already raised considerable protest. *A fortiori*, commercialisation of cells is even more controversial. However, stem cells, both embryonic and non-embryonic, generally undergo many transformations which condition the use to which they can be put in the future. It should be possible to compensate or even reward the work of transformation. Inevitably, financial issues therefore arise as regards any manipulation of stem cells. A first set of ethical problems therefore involves the nature and the limits of acceptable commercialisation of human cells. This examination forms the main body of this Opinion.

Another set of ethical problems is linked to consent. The cell that will be marketed is the cell of a person. Transformation and subsequently the use of that cell therefore require that person's consent. When the stem cell comes from an embryo, the question of the parents' consent is compounded by issues relating to the use for research and therapy of the product of a human embryo.

Finally ethical problems are connected to the inevitable conflict of interest that is raised by biomedical research: the best interests of patients, who aspire to new therapeutic advances and justifiably want private and public research to progress quickly and be supported by substantial investments; the best interests of investors who are ready to facilitate

[1] For the last 20 years or so, stem cells (from bone marrow and blood) have been used as autografts and allografts. Such use has not given rise to any ethical debate since these cells are donated and do not enter into a commercial circuit.

research by providing money on the condition that they may reap the benefits; the protection of people who are the source of the biological material who must be able to consent to the use made of the elements of their body that they donated; the best interests of research for which the prohibition on the commercialisation of products of the human body has effects as regards scientific development; finally the best interests of society which wishes to preserve common standards and the principles on which they are based, underpinned by the respect owed to human beings.

These ethical issues are part of a very specific context. A French national context, regulated by law based on the principle of the non commercialisation of elements and products of the human body. A European context where reticence as regards the commercialisation of elements and products of the human body is far from being incorporated in proposed regulation. Finally, an international context, where there is spirited competition between the various actors, both scientific and economic, in the field of stem cell research.

The products of cell therapy are one of the major prospects in contemporary scientific and medical development. This situation points the way for reflection on the part of the National Consultative Ethics Committee on the general principles which should govern such regulations. It is hoped that this work can provide guidelines to broach the increasingly grave problems which will doubtless emerge as regards the commercialisation of living material.

A survey of the present situation as regards the modes of commercialisation of products and elements of the human body will precede an analysis of the various facets of such commercialisation. The future prospects of research on embryonic or non-embryonic stem cells will be presented with an examination of their possible uses and commercialisation. An ethical consideration of the issues raised will be followed by several recommendations.

1) The present situation

Today, many elements and products are extracted from the living human body. In some cases, the donor receives compensation. It may be pertinent to indicate the types of compensation awarded for these elements and products and the ethical and deontological rules which apply. These indications could serve as a reference for the further discussion of stem cells.

There are some products and elements which can be separated from the human body without any medical intervention nor with any resulting physical damage. Such is the case of hair or milk which are marketed without the need for any special regulation.

This is not the case however for products of the human body which cannot be extracted without medical intervention.

The most frequent example is blood. The law dated January 4, 1993 states that the donation of blood is voluntary, anonymous and free of charge[2]. However, the *Etablissement de Transfusion Sanguine* (ETS - Blood Transfusion Centre) sells the products obtained without profit to hospitals as perishable products (red blood cells, plasma, platelets). The *Etablissement Français du Fractionnement* (EFF Blood Fractionating Centre) sells to the market stable blood products after pooling (albumin, factor VIII, fibrinogen, immunoglobulin, biological products, etc.). These blood products, once they have been processed, become medicines and are marketed. There is therefore a clear difference between blood cells which cannot be marketed as a "profit-making" transaction and blood products obtained by bioengineering so that they become products which can be marketed in the full meaning of the word.

The gift of bone marrow is voluntary and unpaid in the same way as the gift of cord blood. Sperm and oocytes are also donated free of charge, but sperm straws come with a

[2] These principles apply for the donation of whole blood or apheresis donation (plasma, platelets, white blood cells). All such donations required prior consent.

price[3]. Embryos and fœtuses resulting from terminated pregnancies may also be donated for the purpose of scientific research, anonymously and free of charge, after consent has been secured.

For organs, such as kidneys, livers and lungs, they may be harvested from a live or cadaver donor. With a live donor, the donation is voluntary and unpaid, but is obviously not anonymous since the donor is identified. With a cadaver donor, organs (liver, heart, pancreas, intestine, cornea, kidney, lungs, bone, blood vessels) are harvested from brain-dead donors in compliance with the 1976 Caillavet Law. In that event, the donation is anonymous and unpaid. Despite their scarcity, organs are therefore donated free of charge, be they harvested from live or dead donors. They require complex processes which justifies reimbursement to the institution concerned of outlay (costs connected to extraction, transfer, transport and conservation of the graft, generally in the form of a lump sum payment).

We see emerging a fundamental principle. The elements and products of the human body, detached through medical intervention, are freely and voluntarily donated. This does not prevent some of them being sold for a price, once they are separated from the body, or even acquiring the status of a medicine (blood products). Issues as to whether an element of a human body can be equated to a product and whether elements and products can be treated differently therefore have a direct bearing on the question of commercialisation of living material.

2) Definition issues: commercialisation

Since "commercialisation" can serve to designate compensation and the setting of a transfer price as well as sale for profit, we must make clear what henceforth in this report we shall be designating under the term "commercialisation".

What is commercialisation?

Commercialisation is a process consisting in transforming a thing or a product into a marketable object and distributing it within a competitive trading system. This means that commercialisation generally requires two conditions: 1) supply and demand, i.e. a market; 2) setting a price which produces a market balance[4].

It does not seem to be essential for a profit to be made or a profit margin to exist for there to be an act of trade[5], but profit is still the general rule, all the more so when commercialisation is the follow-up of a complex manufacturing process, which is the case in the field of biomedical research (testing on animals, randomised trials, etc.). The commercialisation of drugs materialises a sometimes risky long-term investment.

What would be the meaning of commercialisation of products of the human body?

The general principle according to which products and elements of the human body do not fall within the scope of commerce must be stated at the outset (according to article 16-1 of the *Code Civil* "The human body, its elements and products cannot be the subject of proprietary law"). This principle prohibits the transfer against payment of these elements and

[3] Approximately 50 euros per sperm straw. CECOS (Centre d'Étude et de COnservation du Sperme - French sperm conservation centre) store the sperm straws and spare frozen embryos.

[4] Barter is just a primitive form of commerce; it does not always actually involve true commercial intent: cf friendly swap systems between private citizens, biological sample exchanges between laboratories.

[5] Certain transactions completed by non-profit making organisations (associations, foundations) can be liable for value added tax, even without any lucrative intention, for the simple fact that they are in competition with operations of the same type performed by professionals in comparable conditions. Furthermore, traders may in certain cases be selling at prices which are close to cost (bargain sales), even though loss-making sales are theoretically prohibited.

products by the donor so as to prevent donors selling their own bodies in the form of organs, blood or gametes.

But this principle of non commercialisation is not incompatible with the fact that certain products (for instance, blood components) may, after being processed, be the object of commercialisation leading to profit-making. Nor is this same principle incompatible with the fact that a transfer price is attached to certain products[6] and that their acquisition is paid for as reimbursement to cover the costs of preparation and processing.

It becomes apparent therefore that there is a need to distinguish between the various meanings of commercialisation depending on the one hand on whether the transaction aims or does not aim at making a profit, or on the other hand on the amount of processing or conservation that is required to arrive at the biological product in question.

The presence of profit

When there is no intention to make a profit, commercialisation may describe compensation, at cost price of the outlay on processing, preparation and transformation of the elements of living material. Such compensation, which translates in this case into the setting of a price, seems legitimate if such outlay is considerable. At the opposite end of the scale, profit seeking may give rise to commercialisation if price setting is simply dependent on the ratio between supply and demand, in other words, on the market [7].

The amount of work that has to be done on the biological product before use.

In certain cases, the elements of living material can be used practically as they come or after simple processing (freezing): for example, whole blood, organs harvested and then grafted, sperm, oocytes[8]. Since transformation is minimal, there is reason to believe that money would not be much of a consideration, even though costs are high (transfer of the organ by air, medical teams on standby, etc.). On the contrary, there are other cases where products are used after multiple operations: for example stem cell lines for which there has to be harvesting, processing, culturing, multiplication and finally genetic modification. Product processing is extensive so that it is probable that money would play a major role.

It would seem therefore that the more such manipulation generates "added value", the more expenditure is committed for its development in the experimental stage and the higher are the financial risks, the less biological products undergoing such manipulations can still be defined as "elements of the human body". Also, the more the biological products undergo transformation, the more pressing will be the demand to not just recover financially the expenses incurred to develop them, but also to be able to draw a profit from the sale of these biological products so as to absorb the research expenditure and risks taken by investors.

In the following pages we intend to use the word "commercialisation" as meaning a profit-seeking activity and not just compensation or the price of transfer. In so far as untransformed products of the human body cannot be marketed, the issue of commercialisation will mainly arise for products which are already to a great degree the object of transformation, which is obviously the case of stem cells and the products of cell therapy. Taking account of the value added by these processes and the purpose of covering

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[6] The transfer price is defined by the *Code de la Santé*: price of transfer of blood (art. *1221-9 Csp),* of sperm (*art. L. 1244-5 Csp),* of tissues and cells (*art. L. 1243-1 Csp*), and these rates do not at this point include the possibility of "profit".

[7] As an illustration, a recent report in the French television broadcast "Envoyé Spécial" indicated that the price paid in the United States for the oocytes of a high quality donor (in biological, esthetical and intellectual terms) could be thousands of dollars. There are advertisements in the Harvard University in-house publication for as much as $50,000.

[8] Even though in this case, medical preparation of the woman donor is required and oocyte freezing is particularly difficult and still very imperfect.

costs incurred and previous investment is sufficient reason to refer to commercialisation in such cases.

The link between commercialisation and patentability

For biotechnological innovation, commercialisation is generally connected to the legal protection provided by a patent (it is possible to commercialise a product that is not or no longer patented but is protected by confidentiality; conversely, it is possible to patent a product without being granted the benefit of an authorisation to market it).

The intellectual protection afforded by a patent is generally designed to allow for lucrative exploitation of the patent in the form of sales or licensing agreements. In this respect, there is an obvious link between the debate on patentability and the one on the commercialisation of cell lines, even though the granting of a patent is not in itself an authorisation to use the invention as is stated regarding the patentability of biological material in preamble 14 of the Directive[9].

An invention which is capable of industrial development may confer upon its author an exclusive right of exploitation for a given period of time (generally 20 years). Granting a patent bestows institutional recognition on the invention while it gives the beneficiary the possibility of recovering the expenses incurred to develop the invention (amortisation). It rewards the success of the inventor as it seeks to harmonise his own interests with those of the community.

The ethical justification of filing for a patent is threefold:

- A patent rewards the professional's *worth* and his innovating activity as evidenced by the development of a new instrument for investigation or of a novel technical process (manufacturing, processing, conservation). The patent represents an appreciation of creativity.
- A patent is a method of *protection* of intellectual property by sheltering the expression of the inventor's talent from invidious appropriation by possible competitors who happen to possess rapid and effective means of commercial exploitation of his invention.
- A patent provides the advantage of public *dissemination*. Holding exclusive rights of exploitation of an invention is also an obligation as a counterpart on the part of the beneficiary of such rights to make his invention known and describe it in detail so that others may use it to perfect it and contribute to the development of other inventions based on it; mandatory public dissemination makes patents the primary medium for the transmission of technological information.

In certain cases, however, the use of a patent can create the risk of monopolistic abuse. This unfortunate consequence of patents is due to the fact that exclusive rights of exploitation as provided by the patent may, when its cost is prohibitive, deter attempts on the part of competing firms to improve the patented technique or to evidence other potential functions of the invention. When the implementation of a technique is blocked by one or several patents, the financial investment which competitors would have to make to continue research on the patented invention, if they decided to buy licensing rights to exploit the results of their research could be a deterrent. For example, if a patent is filed for a targeted gene, pharmaceutical companies will prefer to avoid research on that particular gene. This is one of the reasons for which patents are sometimes viewed as hindering research and censured as being contrary to public interest. Ethical issues raised by the patentability of the genome ware raised in CCNE's Opinion n° 64[10] and in a recent Opinion circulated by the German National Ethics Council[11].

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[9] Preamble 14: "Whereas a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial and commercial purposes".

[10] Opinion 64 dated June 8, 2000 on "...a preliminary draft law incorporating transposition into the Code of intellectual property, of a European Parliament and Council Directive 98/44/CE, dated July 6, 1998, on the legal

3) Stem cells: what is new about them?

a) What is a stem cell?

A stem cell is an undifferentiated cell, found in the embryo, the fœtus or the adult organism. It is capable of self-replication (multiplication of identical cells) so as to provide a permanent reserve of cells of the same type and in certain conditions it can differentiate into more specialised cells.

There are several kinds of stem cells, classified according to the various cellular types they can give rise to:

- Totipotent stem cells are capable of enabling the development of a complete individual and of the annexes (placenta and membranes) essential for its intra-uterine survival. This is the case of the fertilised egg (zygote) and of embryonic cells up to the 8-cell stage (blastomere). Beyond that stage, cellular totipotence is lost.

- Pluripotent stem cells are capable of generating all the tissues in the body and are essentially represented by embryonic stem cells (ES cells) present in the inner cell mass (ICM) of the embryo in the blastocyst stage (5th to 7th day after fertilisation). They are not able, however, to form the placenta and membranes which are necessary for viable gestation.

- Multipotent stem cells are present in fœtal and adult tissues and can give rise to several types of cells, but they are already committed to a specific tissular programme. This is the case of hematopoietic stem cells (HSC) in adult bone marrow and fœtal cord blood which generate all the blood cells (red and white blood cells and platelets).

- Unipotent cells can only form a single type of differentiated cell, such as skin keratinocytes or liver hepatocytes.

b) Embryonic stem cells

They were described in 1981 for mice, by Evans and Kaufman, and the first human ES cell lines were derived in 1998 in the United States (J. Thomson). Since then, some hundred lines have been derived and cultured in the United States, Sweden, Australia, Israel, Singapore, India and the United Kingdom. Some human lines have been in culture for several years. They can also be frozen and stored in a cell bank.

Placing these cells in suspension in a culture medium and depriving them of the feeder cell layer, creates the conditions for them to cease to self-replicate and proliferate, instead of which they differentiate.

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protection of biotechnological inventions". The retarding effect on research due to the granting of a patent to a physical or moral person is particularly marked in the field of preventive medicine when the development of a technique for the manipulation of living material (a biotechnology) institutes a monopoly on a method for genome identification (risk of appropriation (through patents) of the tools with which to screen for diseases (which would only be accessible at prohibitive cost).

[11] Opinion by the German National Ethics Council (2005) on the " The patenting of biotechnological inventions involving the use of biological material of human origin". Berlin, www.ethikrat.org. The "confiscation" through patenting of genes which are likely to play a role in the onset of serious diseases could well discourage initiatives by other researchers. The Opinion draws attention to the danger of " ... monopolization of parts of the genome or of specific genes might also impede the development of medicinal products and cause problems with the treatment of patients." (4.1.1.3 Economic aspects, page 20 of the English version).

Certain growth factors can direct ES cell differentiation in a repeatable manner. In this way, certain cell types can be selected by specific molecular marking, isolated and made to produce pure cultures of, for instance, neural or cardiac cells.

The source of human ES cells is invariably the Inner Cell Mass (ICM) of the blastocyst which may have various origins. At the present time, the embryos surplus to IVF (in vitro fertilisation) or ICSI (intracytoplasmic sperm injection), which are frozen and for which there is no longer any parental project, are the main origin. In France, these embryos may henceforth, providing the parents give consent, be used in a research programme under the supervision of the *Agence de Biomédecine* (Biomedical Agency).

c) Embryonic stem cells derived from the transfer of a somatic cell nucleus ("therapeutic cloning"), at present prohibited by the Bioethics Law.

Transferring the nucleus of a somatic cell into a denucleated oocyte allows for the reprogramming of the nucleus and the production of a totipotent cell which resumes the cell division processes which are characteristic of the embryo. At the blastocyst state, it is possible, using the ICM, to derive ES stem cell lines which are genetically identical to the nucleus donor cell.

The feasibility of this technique seemed verified by the work of a Korean team headed by WS. Hwang (2005), but the results turned out to be fabricated. However, the therapeutic efficacy of the approach has been reported in mice in two pathological models (see Annex, Rideout, 2002; Barberi, 2003).

The main advantage of the ntES (nuclear transfer ES) cells is their **autologous** character: these stem cells are particularly suitable for cellular therapy since **there is no risk of rejection.** One of the disadvantages that is most often quoted is the ethical risk raised by the technical similarity between "therapeutic" cloning and "reproductive" cloning as well as the need for a large number of oocytes.

d) Fœtal stem cells

Fœtal tissues, derived from abortions (5 to 9 weeks) contain multipotent somatic stem cells (fœtal neurons have already been used for research in invalidating neurodegenerative disorders such as Parkinson's or Huntington's diseases).

Cord blood also contains hematopoietic stem cells (HSC) in sufficient quantities to restore a child's bone marrow.

e) Adult stem cells

The cells of three organs are endowed with the capacity for life-long constant renewal: blood, the epidermis and the intestine, which demonstrates the existence of active stem cells. Those of the blood and the skin, easily accessible, are already used for therapy.
In recent years, there has been evidence to the effect that other organs or adult tissues (brain, blood vessels, muscles, skin, digestive epithelium, dental pulp, retina, liver, pancreas, etc.) contain stem cells. They are capable of self renewal, of differentiation into the specialised cell types within the family of tissue they belong to, so that they can contribute to the replacement of cells that have died naturally or through injury. They might also be able to differentiate into various cell lines (mesenchymal stem cells).

Be they derived from embryos, fœtuses or adult tissues, stem cells are likely to have a significant therapeutic future. In annex, are listed stem cell characteristics, specificities,

origins, advantages and drawbacks, as well as their possible uses. The modifications undergone by stem cells for therapeutic purposes are varied. The nature and scope of these modifications can help to define criteria to guide ethical considerations and judge whether the cells are still products and elements of the human body.

4) Possible commercialisation: in search of a model for transactions

The possible uses to which stem cells could be put, for fundamental, therapeutic and pharmacological research, and the operational methods involved, now bring us to the need for an examination of the kind of business model that would pertinently apply. Innovation is required in this context. By analogy, we have two extremely different models as regards the regulation of the distribution of biological components: the model given by the harvesting and graft of organs, tissues and blood on the one hand, and the model which regulates the development of proteins for genetic engineering. But neither of these models would seem to be suitable for wholesale application to stem cells and cell lines.

a) Models provided by organ grafts and blood-derived or genetic engineering products

- The business model regulating the harvesting and graft of organs involves three phases:

1 - harvesting: after unpaid donation with informed consent: the medical act of harvesting is independently remunerated;
2 - conserving, securing, processing or transforming: this is a sequence of operations that is liable to payment, as regards the actions, the products and the equipment required;
3 - distribution and use: this gives rise to the establishment of a cost after preparation of the organ or tissue received (graft, transfusion) and the payment of medical actions;

- The business model applied to stable blood-derived products; these products of the human body, obtained by voluntary donation, are nevertheless viewed in the same light as a medicine and are therefore part of the competitive market.

- The business model applied for genetic engineering is the one used for mass production of a compound. Patents are at the core of the commercialisation system used for genetic engineering products.

How could these various models be used for stem cells and cell lines?

As is the case for grafts, in conformity with the non-patrimonial principle set out in Article 16-1 of the *Code Civil*, the donation of human stem cells must not give rise to donor remuneration[12], no more than is the case for the donation of blood, for instance. Donation is made following consent. The medical action may be remunerated. However, the stem cell transformation sequence which is a considerably more sophisticated procedure (not to mention quality and safety tests) is more costly by reason of the expenditure connected to preparation and safety assurance.

Unlike genetic engineering procedures, a cell, once modified, cannot be reproduced artificially. It seems possible that an increasing number of cell lines will be made available for experimental or therapeutic purposes.

Moreover, for stem cells, one must distinguish from the outset between autologous uses (the beneficiary and the donor are one and the same person) and heterologous uses (the beneficiary is not the donor and there could be several, or even numerous, beneficiaries).

With *autologous* stem cells, treatment is customised, "at the patient's bedside". The question then is to evaluate what is in essence a treatment and not a product that could be used

[12] The EGE's Opinion n°16 provides for donor protection in point 2.6: information and consent seeking, non payment with the exception of fair compensation.

by others. But the fact that treatment is only of use for a single person does not exclude *per se* any notion of commercialisation, because to produce such treatment, the stem cells were modified between the time when they were harvested and when they were used, all the more so if a specific effect is sought. (Incidentally, if one day nuclear transplantation becomes a practical reality, the same situation will apply since the cell produced will only be used by the patient who donated the cell nucleus).

Inversely, heterologous stem cells should be kept in "banks" to constitute reference cell lines for research. This "bankable" status normally leads to raising issues as regards their ownership or circulation, establishing a link with compounds in genetic engineering.

Such an analysis leads to the formulation of two major questions regarding the commercialisation of stem cells according to known business models: 1) Would the increase in value and financial protection system linked to patents, be applicable to cell lines? 2) How would stem cell banks be constituted?

b) The patentability of stem cells: should the development and transformation process be patented, or the product and its applications?

This Opinion is not proposing that all the results obtained by stem cell research should be taken as being non patentable. Such a course — largely unrealistic — would be seriously harmful to research.

Furthermore, to prohibit or severely restrict the scope of patent protection for inventions connected to stem cells would lead companies who have already invested in this field to withdraw their interest since it could not be profitable, which in the long term would have detrimental consequences for public health systems.

However, the issue of patents for living material has already been the subject of ample interest and discussion, in particular in connection with the human genome. It takes on a slightly different aspect in connection with cell lines. CCNE had reasserted at the time, as did the European Directive on the patentability of biotechnological inventions, that there was a difference between invention and discovery, since invention bears on the process of obtaining a result and discovery bears on the object itself, existing independently and "naturally"[13]. A similar distinction appears as regards cell lines since it is possible to file for either a product patent or a process patent.

1. A first option would be to consider the patentability of the product (the cells that are modified or produced) as legitimate, the product itself being viewed as inseparable from the process that makes it possible to produce it and make it accessible. This option would have private enterprise or public institutions be given the task — as is the case today for most medicines — of developing treatments for which they have developed know-how that they wish to put to a profitable purpose.

Such an option does however have a practical drawback which is that development of treatment is left to the goodwill of industry (which is of course the case today for most widespread medications) with the risk of blocking research in order to avoid a patented product even if there is every reason to believe that such research could lead to a number of highly beneficial discoveries for patients. In fact, a fairly large number of genetic engineering companies are now emerging.

2. A second option would be to prohibit product patents (cell lines) and to only authorise patents for transformation processes

This option would guarantee a return on investment in the culture and development techniques, but would allow the products that these techniques make possible to be entirely

[13] Cf. Opinion n°27 dated 2.12.1991 on not using the human genome for commercial purposes.

free of access to the results of later research (be they focused on improving the patented processes or obtaining new cell lines). In France and the rest of Europe, there is an exemption applying to research so that it is possible, contrary to American law, to base research on a patented product. However, as soon as exploitation of the result of that research arises, a new patent must be obtained, but its commercial exploitation remains in that case subordinated to the conclusion of a license with the holder of the first patent.

The two options mentioned above do not exclude the setting up of non-profit-making institutions capable of: a) engaging in major research efforts on the basis of other interests besides financial ones and, b) taking an active part in new technologies — as and when they are developed — if they would seem likely to be of benefit to patients. In that case, there would have to be an obligation on industrialists to grant a license for effective methods they may have developed (frequently in a foreign country).

This latter option could be accompanied by the prohibition of commercialising non patented products.

c) Cell banks

Another problem arises with the commercialisation of stem cells for research or therapeutic development, relating to the creation of cell reserves or "banks". If one supposes that numerous cell lines can be developed, it remains to be seen how to ensure their accessibility for various uses.

1. One possibility to make stem cells accessible would be to create cell banks.

One could for example consider a reserve of embryonic stem cells covering the various HLA specificities, which could be used on a "customised" basis since it would be possible to choose cells which are "compatible" with those of the patient in need of treatment. This way of proceeding, which resembles in several ways the creation of an umbilical cord blood bank, could be regulated to organise remuneration of banking services while respecting the rule of not making a profit out of the elements of the human body.

2. A condition for the creation of cell banks is to constitute undifferentiated cell lines, using the collections kept in banks which could be used for therapeutic purposes for specific individuals, possibly in large numbers. One possibility could be the creation of allogenic cell banks, a possible source of very specifically characterised "medicine cells". This is not the case of cells modified "on demand", for one-time use, and a differentiated technical process, the product of a true invention, would be required.

Examples:

. *In vitro* production of red blood cells of a certain blood group using stem cells,

. Adoptive immunotherapy with T lymphocytes expressing frequently encountered HLA molecules,

. In a central nervous system, using nerve cells derived from embryonic stem cells, a situation in which immunological rejection due to incompatibility may not be a problem (which remains to be verified).

In cases of this type, would the inventor of the process be justified in claiming that the processed cell itself and not simply the method used could be commercialised? This is the reason why the issue of choosing a business model arises with stem cells. Could the same development model be used as when a compound is concerned?

As regards the patentability and the distribution of stem cells, various methods have already been adopted and begun to be implemented, either in special institutions — as is shown by the example of WiCell given in the annex — or in international directives touching upon commercial transactions. An examination of these arrangements will provide an opportunity for evaluating on a more specific basis the ethical dimensions of commercialisation.

5) The legal situation today

a. Stipulations regarding the availability of embryonic stem cells.

In France, access to this type of cell is regulated by Law n° 2004-800 on Bioethics (August 6, 2004, promulgation of implementing decrees in February 2006), regulating the availability and distribution of embryos. This latest law authorises research on embryos and human fœtal and embryonic stem cells, through a temporary five-year concession: "Research can only be conducted using embryos conceived in vitro in the process of medically assisted reproduction and which are no longer the subject of parental projects", providing the research "has been authorised by the Biomedicine Agency"[14].

The importation of embryonic stem cell lines for research purposes is also authorised subject to the Biomedicine Agency's approval.

The situation differs from one country to another elsewhere. Some countries, for example Ireland, give unborn children the same rights to life as their mothers. More generally, there are no specific laws governing research on stem cells but regard must be given to more general law governing research on embryos either to authorise it subject to conditions (France, United Kingdom, Sweden) or to prohibit it (Germany, Austria). In certain countries, there is no legislation as regards embryo research (Belgium and the Netherlands), but there is ongoing research.

In most European countries, a legal framework is under consideration.

The Convention for the Protection of Human Rights and Biomedicine, signed in Oviedo in 1997, as yet not ratified in France, refers in article 18 to the fact that it is up to each Member State to forbid or authorise embryo research while stipulating conditions and limitations of such research and prohibiting the creation of human embryos for research purposes.

In the United States, the NIH has set up a register of human embryonic stem cells which is kept up to date to record the existing stem cell lines complying with eligibility criteria (embryonic stem cells obtained from supernumerary embryos for which there is no parental project, free and informed consent by the parental donors, absence of any financial gain for the donors).

These cell lines are available for research only and reimbursement for the expense of preparation and distribution is requested.

On August 9, 2001, President Bush limited financing with federal funds to research using existing stem cell lines. No research using stem cells from new embryos may be financed out of public resources. Private research, however, is not concerned by this presidential decision.

b. Stipulations regarding commercialisation and patentability

Freedom granted for development research in this domain must be provided with the legal protection given to biotechnological inventions using adult or embryonic stem cells. The issue of the patentability of embryonic stem cells is therefore in the process of discussion all over Europe including France, even though patents on similar cells have already been granted in the United States.

The present situation and filings are summed up in Opinion n° 16 of the European Group on Ethics in Science and New Technologies (EGE) dated 7 May 2002: over 2000 claims for patents have been filed worldwide for human and non human stem cells, of which a quarter concerned embryonic stem cells. These claims concern:

- *either processes*: for isolation, enrichment, culturing, genetic modification, induction of differentiation, induction of adult stem cells for retrodifferentiation or

[14] Articles 25 and 27

transdifferentiation and the transformation of somatic cells into stem cells,

- *or products:* involving stem cells, stem cell lines, differentiated stem cells and genetically modified stem cells.

Two different approaches seem to be adopted in existing legal documents.

In Europe, the European Directive 98/44 dated July 6, 1998 on the legal protection of biotechnological inventions proposes accepting the patentability of stem cells. This directive has now been transposed in almost every member country of the European Union. It was the subject of the CCNE's Opinion n° 64 dated June 8, 2000 as regards the limitations on patentability of living material. The Opinion recalled that knowledge of a gene sequence cannot be regarded as an invented product and is not, therefore, patentable.

An Opinion of the European Group on Ethics in Science and New Technologies (EGE) dated May 7, 2002 gave an ethical interpretation to this directive as regards the specific problem of stem cells. Directive 98/44 and the EGE Opinion broadly open the way to the possibility of patenting not just processes, but also products — the cells themselves — with some restrictions.

These two texts are considered below and in further detail in the annexes.

The European Directive 98/44 dated July 6, 1998, is exclusively aimed at harmonising patent law in Europe in the specific field of biotechnological inventions which it accepts.

Article 6 of the Directive, however, provides for a certain number of exclusions from patentability for reasons pertaining to "*ordre public* and morality". It specifies in particular that inventions requiring the use of embryos for industrial or commercial purposes are not patentable, but in para. 42 of the preamble it is added that such exclusion does not affect inventions for therapeutic or diagnostic purposes.

Although industrial and commercial uses of human embryos[15] are excluded from patentability by virtue of article 6 of the Directive, this prohibition does not apply to embryonic stem cells which can not longer be considered as embryos. Such cells can therefore be the subject of process or product patents[16].

EGE Opinion 16 on the other hand states that article 6 of the Directive does not provide any definition of embryos concerned by the exclusion. Therefore, certain embryos should be exempted: non viable embryos[17] (which cannot lead to a birth) such as those created by parthogenesis. However, a limitation arising out of Article 6§2a seems to be established: "...are not patentable "Processes for cloning human beings" so that, notes Opinion n° 16, should be excluded from patentability processes for the creation of human embryos by cloning with the purpose of obtaining stem cells.

However the issue of consent to ulterior exploitation by a patent is not to be found in texts on patent law and does not appear in the articles of the Directive: only paragraph 26 of the preamble mentions such consent and recommends it.

EGE Opinion n° 16 therefore limits the scope of patentability of cells by making two distinctions between elements of the human body and in consequence on their possible patentability, depending on whether or not the elements of the human body are detached and whether the cells are modified or isolated.

According to European recommendations, the patentability of adult and embryonic stem cells would be possible depending on the status conferred on cell lines: if they are products of

[15] EGE's Opinion n°15 dated November 14, 2000 on "Ethical Aspects of Human Stem Cell Research and Use" recommended that measures be taken to prevent the commercialisation of human embryos or of tissues from dead fœtuses.

[16] A decision to that effect, Paris Tribunal, January 21 2003, n° 0207626/6 confirmed on appeal by order dated May 9, 2005, 3e ch B, n° 03PA00950.

[17] Scientifically, their capacity to achieve birth is supposed to be very weak for a cloned embryo and close to zero for parthogenesis.

the human body which are simply *isolated* and left unmodified, they are not patentable; if they are products *derived* from the human body, that is cell lines derived from isolated stem cells, obtained with a technical process, *in vitro*, they cannot be viewed as natural stem cell lines, and are therefore patentable.

Product patents for stem cells should therefore be obtainable, according to the Directive, on condition that the cells are considered to have been "processed and modified". Similarly, process patents for the products of cell therapy should also be granted once the technical conditions are filled.

Nevertheless, it can be expected that the cell lines themselves would cease to comply with patentability criteria because of insufficient novelty, invention, or industrial application (this because following chromosomal modification, they run the risk of becoming dangerous and unusable), but that is a technical problem, solved by patent offices on the basis of regulations.

In France, transposition of the Directive was delayed because of a degree of reluctance. The matter was referred to the European Court of Justice in the course of an action for failure to fulfil obligations, which led to the ECJ's ruling against France on July 1, 2004, (Aff. C-448/03).

The provisions of the Law on Bioethics voted on August 6, 2004 as a result of the transposition of Directive 98/44 were a compromise solution and attempted to temper the scope of patents. CPI Article L. 611-18 transposes differently Article 5 of the Directive by stipulating that "only an invention constituting the technical application of a function of an element of the human body can be patent-protected". Nevertheless, significant divergence between the formulation of the above text (and that of CPI Article L. 613-2-1) and Article 5 of the Directive dated July 6, 1998, is problematic. However, the Commission is still evaluating the consequences of one or the other courses and its position may change over time.

II. Ethical examination of issues raised by the possible commercialisation of stem cells.

The possible commercialisation of stem cells and other cell lines raises many ethical problems. Before considering the subject and outlining general guidelines for solving these problems, it is important to identify the criteria which may have ethical dimensions in this respect.

Some criteria are ontological and bear on the status of elements and products of the human body. Others concern the degree of modification undergone by the stem cells. Yet more are connected to the cells' origins, to the nature of consent given for their removal, to the purposes for which they are to be used and to the kind of regulation to be provided.

Ontological criteria: what of the nature of the elements for commercialisation?

Depending on the manner in which the biological entities concerned are defined[18], commercialisation takes on different dimensions.

If the biological material is unprocessed, as is the case for stem cells, embryonic or otherwise, commercialisation which can lead to a profit-making endeavour may raise significant issues in view of legal provisions and moral reprobation surrounding any commercial use of the human body. This ethical difficulty is due to the "living" nature, not simply organic or chemical, of the cells concerned and what defines "life" is the capacity to

[18] The expressions "biological entities" or "biological material" designate the products and elements of the human body.

reproduce an identical being. It is also because this life is human life that ethical questions arise, which would not be the case with animal biology.

Inversely, taking the case of a chemical compound, ethical and legal problems regarding their possible commercial use can be dealt with according to the order regulating material things and possessions.

Between the two, there is a difficult grey area, somewhere between what is biological and what is chemical, for which most of the ethical problems arise. This grey area includes the intermediary entities, biological products, but modified to such a degree that they have partially lost their biological status. These are, for example, cell lines, products of cellular therapy, or of cellular and tissular bioengineering, etc. For such entities, the question of whether they can be considered as biological realities or pharmaceutical specialities or manufactured medicines remains open. In other words, do the manipulations to which these biological realities have been subjected change their very nature?

This is comparable to products derived from human blood (immunoglobulins, factor 8) which have been modified to such an extent that they are viewed as products detached from the body. Can this be the case for stem cells, be they of embryonic, fœtal or adult origin? When do such cellular elements become sufficiently detached and different from the human body for them to be the object of trade? It seems quite impossible to define either boundaries or criteria.

Another criterion which is closely connected to ontology is related to the type of relationship existing between the entity in question and a human individual viewed holistically. It is obvious that an organ is not related to an individual in the same way as a cell or a molecule. It would seem reasonable to consider that the closer is the integration with the individual as a whole, the more the possibility of commercialisation would raise ethical problems.

It is therefore legitimate to consider that one of the main concerns in the ethical debate on the commercialisation of stem cells will relate to the ontological status of the entities involved (whether cells are unprocessed or modified, what proportion of the human body is in question) and their degree of integration within the person.

Criteria connected to the degree of human intervention, processing and modification: product of the human body or artificial product?

Depending on whether the biological entities under consideration are unprocessed or have undergone a greater or lesser degree of modification, ethical problems connected to their commercialisation are more or less acute. We find here a criterion relating to the degree of modification to which the biological material is subjected (this criterion overlaps to a certain degree with the ontological criteria referred to above, to the extent that the degree of human intervention can modify the status of the entities concerned).

It is important to define pertinent thresholds so as to appreciate the various levels of intervention required to obtain the desired cells. Minimal intervention, for example, would consist in processing a cell for the purpose of conservation. Maximal intervention would involve obtaining a cell by nuclear transfer. Most of the interventions on stem cells lie between these two extremes.

In such a transformation process, the first step is harvesting, which supposes some form of direct relationship to the source which may, or may not be modified as a result. The process of harvesting does not modify the biological entity's status.

Further intervention is exemplified by processing, comparable to what is practised today with organs, blood and sperm, for the purposes of conservation and security. The ontological status of the biological product is not thereby changed, so that it is not what could properly be called a modification. In other words, if commercialisation of the source product is an issue, this will also be true for commercialisation of the processed product. The fact of covering costs arising out of, for example, the procurement of safe conditions for optimal conservation of the product will not, in itself, raise ethical problems.

Other types of intervention are connected to what can be called manipulation, — on the condition that the word is understood to be free of any negative interpretation. This is the kind of intervention that is undertaken when a laboratory seeks to obtain a modified cell line. A certain number of technical operations which come at a cost may be necessary to process these entities. They include:

- *Amplification of the number of cells*
- *Transformation* as such or induced modifications to internal characteristics for experimental or therapeutic purposes
- *Combination* with other entities of the same level
- *The concept of differentiating stem cells into functional cells of a given tissular type.*

In each of these cases, there are safety and traceability requirements which must be met.

One final operation consists in transferring these biological products, once they have been transformed, into a tissue or organism. This is theoretically the ultimate phase which may be for experimental or therapeutic ends. As such, this last phase is not properly speaking a phase of transformation of the product, but it has an effect on the ethical appreciation of its commercialisation.

Criteria connected to the type of relationship between the product's source and the product's user: should autologous and heterologous cases be treated differently?

Should the prospect of commercialisation and the ethical problems arising as a result be viewed in a different light depending on whether beneficiaries are or are not themselves the source of the sample?

If donor and beneficiary of a stem cell are one and the same person (a situation which mainly arises in the case of adult stem cells), a price is only set because of the cost of isolating and securing the characteristics of a cell. This is autologous therapy. Even in this case, a price may be set in so far as the cells undergo *in vitro* modification. Commercialisation based on the development of an ingenious process would seem legitimate. As an example, should at some point in the future nuclear transfer become an effective practice, at some point between harvesting and before use, a highly "modified" cell will make its appearance, but it will be used only by the patient who was the donor of the cell nucleus. Even in this case, however, commercialisation is still limited to the process.

Conversely, when the beneficiary and the donor are not the same person and therapy is heterologous, standardisation of the process may raise the issue of commercial exploitation. Attribution to a fully identified beneficiary which limits standardisation is tantamount to the previous case of an autologous donor. A bank holding multiple beneficiary cell lines could raise the possibility of commercial exploitation of the product. The autologous or heterologous status will not change the fact that it is still the same product for a single person or a number of persons. Simply, the bank status will liken these stem cells to blood banks and

not to medicines. There is a clear indication here of the temptation to drop the banking-for-conservation status in favour of the financial banking status.

Criteria connected to the origin of the stem cells: does embryonic, fœtal or adult origin create a difference as regards commercialisation?

Does the origin of the cells have an impact on the definition of the ethical problems which arise out of a possible commercialisation?

When the origin of the cells is an adult, a fœtus or cord blood, ethical problems are solely confined to the issue of whether it is possible to create commercial value using products of the human body.

If the origin is the embryo, to the above problem is added the decisive issue of whether it is morally acceptable to use embryonic biological material for research or for therapy.

Certain people are opposed to any use of embryonic cells leading to the destruction of the embryo. For those who consider that it is not morally acceptable to perform research on embryos or to use them for therapeutic purposes, *a fortiori* the possibility of establishing cell lines sourced from embryonic stem cells is reprehensible. On this point, the French laws on bioethics took a stand. They gave legal status to research on the embryo. Nevertheless, knowing if the stem cells are, or are not, embryonic has an impact on the way in which the ethical issue of commercialisation of stem cells and other cell lines can be formulated.

The criterion of consent: can consent give legitimacy to the commercialisation of what should otherwise be excluded from commercialisation?

Insofar as the unprocessed biological material is donated by a person and it can then be used nonselectively, the question of that person's consent to using what is issued from his or her own body and to the commercial exploitation that could be made of a product of his or her own body becomes crucial.

However, securing consent at the time when the biological material was initially donated does not suffice to settle all ethical problems. In the case of reiterated use of biological material, particularly if this use is for new and different purposes to those initially planned, the question arises of whether consent is still valid[19]. Would it not be preferable to consider that consent fades away with successive derivations and that uses made of biological material at the end of the journey no longer benefit from a shred of consent? Should some form of reiteration be made of the request for consent at each new use, or is it right to agree that distance *de facto* creates a legal distinction? Would not any kind of commercial use raise grave ethical difficulties if it could no longer be justified by approval and consent?

Clearly, the issue of consent given by the source person differs in the case of adult stem cells and embryonic stem cells, since it will be parents who are consenting to any use made of embryonic cells. But even in a case of this nature, is it ethically acceptable to consider that consent remains valid for undefined uses without such consent being regularly updated?

[19] CCNE Opinion n° 77 dated March 20, on Ethical issues raised by collections of biological material and associated information data : “biobanks”, “biolibraries”.

The criterion of end use: does a therapeutic purpose, rather than a scientific or pharmacological purpose, have an impact on the prospect of commercialisation?

The question of commercialisation of stem cells cannot be raised without some consideration of the purposes for which the introduction of commercial value is intended.

One purpose is therapeutic. When the introduction of monetary worth relates to the reimbursement of the processing costs required to enable therapeutic uses, be that for a single person or for several, the financial element appears as the condition without which a beneficial therapeutic use of this kind could not take place. When, however, the introduction of financial value aims not only to enable therapy but also to make a profit (even though the development of such therapies would not be accessible without the presence of a commercial dimension) the question of whether the introduction of monetary value raises or does not raise an ethical problem becomes crucial. That is why the nature of the link which exists between the introduction of a monetary dimension and the possibility of therapeutic use is decisive.

Another purpose is scientific. It is difficult to argue against the obvious value of developing knowledge on the use of stem cells. It is conceivable that the intervention of financial value often conditions the existence of scientific achievements, such as the development of research and of knowledge. If such is the case, the ethical issue raised by the introduction of a monetary dimension, in the form of investment, in the use of biological material cannot but take into account the intrinsically useful nature of the achievement, that is the increase in the corpus of knowledge.

A third purpose is medical and pharmacological. It appears when the introduction of a commercial value has the effect of enabling the development of pharmaceuticals and medicines which, instead of being aimed at specific patients, are of benefit to many people. In that case, the end purpose can be considered to be beneficial and commercialisation seen as a profit-seeking occupation becomes a necessary condition.

Other purposes can be considered as regards the use of stem cells, such as cosmetic ones which, unlike those previously mentioned, cannot be seen as obviously positive. When even in cases where the purpose considered is indisputably positive (therapy, science, medicine) the introduction of commercial value still raises ethical issues, this is *a fortiori* the case when the end purpose does not include positive characteristics.

Finally, it is important to state once again that any reproductive purpose must be excluded from the outset. For legal and ethical reasons which have already been expressed on numerous occasions, no manipulation of the embryo or of embryonic stem cells can aim at the birth of a human being.

Criteria connected to interests under consideration: interests of patients, commercial interests, national interests

The introduction of commercial value into the numerous transformations which affect stem cells is not limited to providing profits for the pharmaceutical industry. Many other interests are involved. Depending on their nature and their proportional importance in relation to each other, the ethical question of commercialisation takes on a different appearance.

The first interests that must be considered are those of patients. If therapy is developed through financial investment patients benefit directly from the possible introduction of commercial value into the process. When such interests are powerful, because patients are numerous or more seriously ill, they bestow upon the introduction of this commercial value — which is the condition of the development of a therapy — an even more positive value. In such a case, a form of commercialisation of stem cells could have beneficial consequences in the service of patients' interests.

Other interests concerned are commercial interests connected to profit-seeking, and these do not have any immediately obvious ethical value. But to the extent that these commercial interests can condition investments without which no therapy would have been possible, their presence may lead to positive consequences. For this reason, to decide that their very presence must be the object of disapproval at the outset is a little hasty and counterproductive.

Other more general or abstract interests are linked to the development of research or to the ranking of national laboratories in the global league-table for biotechnological research. A decision to develop national or European research in this field can lead to the promotion of certain types of research, which requires financial investment. The assessment of interests of this nature cannot be detached from their financial aspect.

It becomes clear therefore that taking into account the interests involved (interests of patients, financial interests and interests of national research) modifies the configuration in every case of the problem raised by the introduction of commercial values. It cannot be said simply because economic interests enter into the equation that commercialisation is immoral. To prohibit any kind of commercial added value could be contrary to the interests of the public at large and those of patients. The presence of such interests and the weight given to them have an impact on the ethical appreciation of stem cell commercialisation.

Criteria connected to the mode of commercialisation: private or public sector? competition or monopoly?

Accepting for the sake of argument that the intervention of commercial value is necessary for the creation of new therapies, does the fact that such intervention is based on private or public initiative create any moral difference?

On could consider that public interests necessarily serve the public at large whereas private interests give first place to private investors. It is true that public funds are State funds, are not supposed to serve any partisan interests and are intended to promote the interests of the public. Profits which accrue following the investment of public resources are of benefit to the community as a whole. On the contrary, private funds are provided by particular companies or individuals and the possible profits will go to specific companies and individuals. Public interests are not directly of concern in these profits, except very circuitously. However, one must not be blinded by this dichotomy which would tend to put morality on the side of public investment and immorality on the side of private investment. To begin with, as regards development, public and private investors often work in partnership and tend to behave identically. Furthermore, private investment can be made compatible with very strict specifications and be mindful of public interest.

When a public monopoly is the source of investment, the possibility still remains that the introduction of commercial values, while obeying profit-seeking motives, could take place according to mainly rigidly defined directives and without sufficient investment. This kind of intervention tends to select *a priori* the interests it seeks to serve and in most cases might well be insufficiently reactive to market changes. Or on the contrary, such investments might be

inclined to stick to promising research avenues even when they seem unlikely to lead to any immediate profit.

In a competitive environment, however, investment options will be defined according to the laws of the market, with no single project manager, so that research avenues which hold no promise of profit would be abandoned while substantial amounts could be invested in more promising research possibilities. But some fundamental research, which is not very profitable in the short term, might be entirely neglected by a competitive research environment as might be also the case for rather unprofitable therapeutic research (rare diseases).

The reality of international competition is often mentioned to justify the abandonment of ethical demands. However the increasing availability of products provided free of charge by public or private non-profit initiatives is leading the way in permitting the coexistence of several types of market. States and companies who are making their products available to the public at large draw a moral benefit from that action which may also lead to economic benefit.

Criteria connected to access to healthcare and to distributive justice: can commercialisation respect distributive justice?

A set of fundamental criteria regarding the introduction of commercial value into the exploitation of stem cells and other cell lines is connected to the access to healthcare that such commercialisation may lead to.

Depending on whether the introduction of financial value is or is not compatible with extensive access to the therapies which are developed, its ethical appreciation will be more or less positive. In the case of patentability, for instance, the prospect of being granted a patent will be the condition for the investment of substantial amounts of money. The investment might lead to the development of medicines which will be protected by a patent during several years before becoming accessible generally. Depending on the length of the period of exclusive exploitation, depending on whether the disease affects rich countries where patients can afford to pay for therapy, or poor countries where patients are unable to pay, the ethical issue will appear in a different light.

More often than not, without investment there is no therapy and without therapy, there is no possibility of cure. For this reason one cannot disqualify out of hand for ethical reasons any introduction of financial value.

From another angle, if a certain form of justice is not respected in the distribution of healthcare, it becomes difficult to consider that the introduction of a financial value has any moral effect whatsoever. The way in which access to healthcare and an equitable form of distribution of healthcare are ensured play a decisive role in appreciating whether the introduction of financial value is morally acceptable.

In conclusion, this Opinion reiterates that it is necessary to distinguish between two meanings of commercialisation: the first of these covers possible compensation to the initial donor and the expenditure incurred for harvesting, processing, transforming and preserving to the highest safety and traceability standards; the second designates a profit-seeking activity entailing a cost and a benefit. This second situation is what we shall be designating by the term "commercialisation". It is to that situation that the ethical guidance which follows applies.

A reservation must be made at this point. If the introduction of money depends only on the good will of investors and obeys no rule, there is reason to believe that commercialisation could disregard ethical criteria. Inversely, if commercialisation is based on rules and governance plans which contribute to the safeguard of public interests, the moral issue relating to the introduction of financial value will appear in a very different light. That is the reason why the prospect of regulating the various forms of commercialisation can modify the

moral appraisal that is made of it, to the extent that such regulations aim to respect specifications defining the demands of the community and are in phase with the public good, and to the extent particularly that they contribute to setting strict limits to regulate possible commercialisation.

III. The main recommendations

1.

The source element, the stem cell, defined as an element or product of the human body is, as a general principle, neither patentable nor open to commercialisation. CCNE reaffirms in this Opinion the fundamental ethical principle according to which neither the human body nor any of its elements or products can be the "subject of patrimonial law", nor give rise to transactions involving direct or indirect remuneration of the donor, nor revenues of a commercial nature accruing to any institution. The dual foundation of this principle is: on the one hand that the body, its elements and products, are not "objects" (and cannot give rise to exploitation, for whatever purpose); on the other hand, any kind of exploitation would be all the more unacceptable if it involved for a human being suffering, risk — possibly to life — and disregard for human dignity. The principle that the human body, its elements and products are non patrimonial is absolute in the eyes of society and pertains to *ordre public*. Neither the person concerned nor any donor (individual or institution) can be regarded as the owners of a human body or of one of its elements and products. **In so far as stem cells derived from the human body are elements of the human body, they cannot as such be the subject of commercialisation or give rise to remuneration.**

2.

This principle, however, does not prohibit the remuneration, including in commercial form, of:

- on the one hand the actions, interventions and operations that accompany or follow the harvesting of cells, in particular the various transformations they may be subject to,

- on the other hand, the various uses that the transformed product could be put to after far-reaching modification.

3.

When ingenious human action has sufficiently modified a cell for it to become a product which has lost a cell's phenotypic and functional characteristics, the question of whether the product thus obtained can be commercialised should be submitted to an Agency such as the Biomedicine Agency.

4.

When transformation has radically modified the nature of the product, the general rule is that the modified element can be commercialised within the bounds of patentability of the process and subject to the limits and conditions outlined above. Were that element, having lost its status as element of the human body, to be reintroduced into a human body, it should be comparable to a "biomedicine".

5.

The fact that cells are of embryonic origin is no reason for exemption from the above recommendations. However, there is a risk which must be kept in mind that the embryo could

be treated like laboratory material or a medicine. This comment does not imply any disapproval of research on embryonic stem cells. The possibility — at this point excluded by law — that stem cells could be obtained by nuclear transfer would raise an ethical issue as regards their commercialisation in the same terms as the commercialisation of embryonic stem cells, if such cells were to be considered as elements of the human body and not as simple laboratory artefacts.

6.

The rules governing the granting of process patents for the use of stem cells should be fairly restrictive so as to avoid hindering new research developments or giving exorbitant rights to inventors, disproportionate to the quality of the invention and detrimental to public health and access to healthcare. Patents granted with too broad a scope could have that effect. The obligation by law to enter into licensing agreements would seem advisable.

7.

Informed consent by the donor remains essential. Donors must be able to have their say regarding the use made of their cells. The new principles of ethical trading relying on information given to the donor, to the participants in research and to the user could encourage market regulation and open the way to a method of exchange based on donation, which would make it clear that an ethical component can change the nature of the market and lead to a modification of the behaviour of commercial competitors.

8.

Other conditions for the possible commercialisation of modified stem cells are connected to the accessibility of medicines derived from them. The cost of therapy must permit patients in need to have access. This concern, as well as other public health requirements, define the limitations put on the commercial use of cell-derived products.

9.

The creation of cell banks, similar to existing umbilical cord blood banks, should be considered. The patentability of processes which enable such cells to be obtained is sufficient to guarantee the development of pharmaceutical research. Inversely, the possibility of patenting stem cells as products would violate the principle of the non commercialisation of products of the human body, unless they have become derived products which no longer retain the characteristics of a biological product.

Conclusion

The recommendations listed in this Opinion are based on the principle of the non patrimonial nature of the human body and that the products of a human body cannot be the object of lucrative commercialisation. These recommendations could be viewed as an obstacle to the development of certain kinds of research, in so far as such research would be founded on the use of cells which, after manipulation, were to be multiplied and used, or even re-implanted, without losing their original nature. CCNE is aware of this, but considers that strictly regulated patentability acquired solely for the process is the optimal condition to enable the development of research and of new therapies in compliance with the principles which have been defined.

This Opinion attempts to reconcile the present and future demands of therapeutic progress while it remains respectful of the founding ethical principles under examination.

This Opinion was approved by the members of the Committee as a whole with the exception of Marie-Thérèse Hermange who expressed her total disagreement with the document. Some members expressed reservations in complementary contributions.

June 22, 2006

COMPLEMENTARY CONTRIBUTIONS BY CERTAIN MEMBERS TO THE OPINION ON THE COMMERCIALISATION OF STEM CELLS

1

Observations on the conclusions of CCNE's Opinion on the commercialisation of cell lines.

Following a detailed report, the recommendations included in the CCNE Opinion on the Commercialisation of cell lines call for the following comments by certain members of the Committee:

1 - The Opinion recalls two fundamental ethical principles: the non patrimonial nature of the human body, of its elements and products on the one hand and on the other, the need to obtain informed consent from donors before any use is made of their cells. The report itself lays out the issues which are raised here by the application of these principles. However, recommendation n° 2 is still not satisfactory as regards the non patrimonial principle and contradicts it. It states that it "*does not prohibit the remuneration, including in commercial form, of: on the one hand the actions, interventions and operations that accompany or follow the harvesting of cells, (...) and on the other hand, the various uses that the transformed product could be put to after far-reaching modification.*" The recommendation therefore accepts the commercialisation of cell lines. Furthermore, it leaves unresolved two issues which would, at the very least, require clearer response.

- Will national ethics and deontology agencies be given the right, and according to what criteria, to appreciate whether a cell has been sufficiently modified to be considered as no longer an element of the human body?
- Even if the sampling of initial stem cells is not remunerated, the operations which follow and which would be remunerated, are not free of charge; they would constitute the essential part of the profit margins thus indirectly encouraging commercialisation (as is demonstrated by the analogy of human blood donation which does not in fact prevent the commercialisation of blood derivatives). In this practical situation, would the distinction posited by the Opinion between initial cells and transformed cells be really functional?

One might well fear that recommendation n° 2 and the ones that follow it are too imprecise to regulate supply and demand, or even the patenting of cell lines including human stem cell lines.

Inversely, as regards adult stem cells, there is legitimate justification to allow the remuneration of actions, interventions and operations which precede, accompany or follow their harvesting and the creation of cell banks as is already the case for umbilical cord blood cells. The question remains open as to whether the transformations which they undergo could

deprive these cells of their original nature and possibly justify commercialisation of these derived products.

2 - Secondly, obtaining certain human stem cells is in itself the source of serious ethical issues. The embryonic stem cell lines can only be obtained by harvesting them from human embryos which are then rejected. These embryos are purely used as a means to procure stem cells and are then treated *"like laboratory material"* to use the very wording in recommendation n° 5. This raises serious ethical objections in the name of human dignity and the report notes that some of its members feel very strongly in this respect. Furthermore, it is important to remember in this connection the point CCNE had underlined in its Opinion dated October 15, 1986: "*Not only should the anthropological, cultural and ethical meaning of the beginning of life be taken into consideration, but also the consequences or upheavals that certain practices or research could imply for the overall representation of the human person".* The way in which we treat future human beings obviously has weighty repercussions on our perception of the human person and therefore on our behaviour. Recommendation n° 5 notes that such a risk exists, but does not devote much attention to it and it would seem that, without actually saying so, this is crossing a very important line into a trivialisation of embryo research, at some distance from legislative precautions and disinterested motivations that were upheld so far. Their embryonic origin demands that harvesting and using stem cells be excluded, and *a fortiori* any remuneration or commercial transaction attached to such transactions.

3 - For the same reason, recommendation n° 9 considering "*the creation of cell banks*", justifiably gives rise to grave disquiet, since it provides for no distinction between the various human stem cell lines which would be "banked". Such a recommendation could be interpreted as meaning to encourage a proliferation of harvesting of cells from human embryos in vitro and giving improper legitimacy to opportunistic research programmes or even those with purely lucrative aims (cosmetic for example).

The above contribution, drafted by Madame HERMANGE, Monsieur de DINECHIN and Monsieur ROUVILLOIS, firmly emphasizes these ethical objections.

2

The simple designation of what can legitimately be commercialised does not suffice to cover the ethical considerations connected to commercialisation. The ethical outlook of each of the actors involved in stem cell research can have a far reaching influence on the way in which access is given to the useful applications of such research.

The meaning attached to "market" and "free competition" has evolved on the basis of ethical considerations that go beyond traditional ideological divides been public and private, with the opposition between a vision of public monopolies aiming for free access but slowing down innovation by preventing the full play of competition on the one hand and of a free-market with open competition promoting innovation solely through profit-seeking, on the other. The coexistence of various kinds of competitive systems — free gifts, non-profit making sales,

profit-making sales — is an incentive for the development of innovation, equity and for both producers and consumers to act more responsibly, thereby adding an ethical dimension to the market independently of concerns based entirely on economic profitability.

To give just a few examples: 1) the decision for ethical reasons taken by the scientists working on the Human Genome Project to publish all the gene sequences without taking out patents; 2) the development by researchers of freely-accessible high level biomedical scientific publications (the PLoS/Public Library of Science scientific journals), which has completely changed the face of a market which up till then was entirely composed of publications selling (at a very high price) the results of public research; 3) the development by researchers and users of the free software *Linux* in competition with (and now complementary to) *Microsoft* software sold for profit, etc.

So we find that innovation is not necessarily linked to economic and financial gain and that original individual and collective initiatives, powered by ethical considerations, in particular the free sharing of the results of research, can combine innovation and accessibility and thereby increase both the possibility of free choice on the part of users and distributive justice. But clearly such actions cannot be launched unless the market players understand that their ethical reflection can lead to changing the market. It is perhaps at this level that deontological and ethical considerations differ most visibly.

For the above reasons, CCNE could have made the following recommendations:

1. CCNE considers that it is important to make the actors of research aware of the need for reflection on the major role they may be playing in the regulation of the ethical dimensions of the market when they select the method for making available the applications of their research. CCNE encourages reflection that would give priority not just to technological innovation but also to innovation leading to the integration of the ethical dimension, thus encouraging researchers to accept more responsibility in the future and accessibility of the products of their work. In other words, the fact that to file for a patent and to engage in profit-making commercialisation is authorised should not be taken as automatic encouragement to take such a course.

2. Donors are essential participants in these innovations, be they the donors of their own cells in the case of adult stem cells, or the parents for embryonic stem cells. CCNE considers that the concept of free and informed consent, which is at present one of the essential components of biomedical ethics, should not solely depend on the provision of information on the scientific project and the possible biomedical applications, but also on the possibility or otherwise of these applications being put to commercial profit-making or non profit-making use. Excluding donors from any form of commercial transaction because of the non patrimonial nature of the products of the human body should not lead to excluding donors from any choice in the commercial or non commercial applications which could be made as a result of their donation. Donors of cells should be able to choose, on the basis of the information provided to them, the type of development and accessibility of innovations in which they would like to participate, thereby becoming fully-fledged actors in the regulation of the ethical dimensions of the market.

3. Empowering each of the actors — donors, researchers, administrators of research institutions and non profit-making foundations, etc. — and debate on these subjects with patients' associations, international organisations, representatives of the pharmaceutical industry and society as a whole, should encourage the development in this field, as in other domains touching on biomedical research, of an ethical vision for putting on the market applications which are beneficial to health in which profit-making commercialisation would be just one option among others. Choices should be justifiable to society in terms which are not only concerned with economic profitability.

Jean-Claude AMEISEN

ANNEX I

THE DIFFERENT KINDS OF STEM CELLS

1) Embryonic stem cells

Background

The idea of using EC cells as a source of cellular therapy had been under study since the 1970s, but their tumoral origin and the frequent presence of chromosomal anomalies did not recommend them for this task. By culturing, in the same conditions, mice embryos, Evans and Kaufman (1981) obtained pluripotent cell lines from the inner cell mass (ICM) of the blastocyst: ES cells.

In 1998, James Thomson and co-workers derived the first human ES cell at the University of Wisconsin-Madison in the United States from the ICM of a blastocyst donated by a couple who had undergone in vitro fertilisation. Since then, over a hundred cell lines have been derived and cultured in the United States, Sweden, Australia, Israel, Singapore, India, Korea and the United Kingdom.

Production

The blastocyst is the ultimate stage in development of an embryo before implantation into the uterus (preimplantation embryo) and in humans corresponds to days 5, 6 and 7 after fertilisation. The blastocyst is made up of 50 to 250 cells, the majority of which line the cavity that was formed in the centre of the blastocyst and filled with liquid (blastocœl). These cells, called the trophectoderm, will develop into the placenta and membranes. At one of the poles of the blastocyst, a group of 15 to 50 cells differentiate and are the origin of the fœtus (the inner cell mass). They go on to produce the three primitive layers of the embryo: ectoderm, mesoderm, endoderm, the cells and tissues that derive from them and the germ cells.

The first step required for the production of ES cells is to isolate the ICM, by mechanical, chemical or immunological means. In order to harvest the embryonic stem cells, the external membrane of the blastocyst is perforated, the inner cell cluster which contains the stem cells is removed and transferred to a Petri dish containing a culture medium. The blastocyst is then destroyed and cannot continue to develop, but the embryonic stem cells can be cultured *in vitro*. The ICM cells, dissociated or not, once they are put in culture on a layer of "feeder" cells, attach themselves to that layer, proliferate and after a few weeks produce colonies of ES cells, which continue to reproduce while maintaining their lack of differentiation. Some human cell lines have been kept in this way in culture for several years. They can also be frozen and stored in a cell bank.

To be successful, the culture needs, apart from the growth medium, so called "feeder" cells (fœtal fibroblasts). Scientists are now working on obtaining stem cell lines grown on human feeder culture material, or without feeder cells and in perfectly defined culture media.

Improving culture conditions of ES cells is a capital issue in the development of cellular therapy strategies based on the use of stem cells. It must be possible to amplify and control proliferation, maintaining the pluripotent nature of cells and also their chromosomal stability[20]. The sanitary safety of the culture must also be ensured through adjustments to

[20] *Several examples have been reported of anomalies after several weeks or months, Draper et al, 2004; Inzunza et al, 2004*

laboratory techniques and eliminating feeder cell layers or products derived from animal origins.

The second phase, that of differentiation, occurs spontaneously if the ES cells are suspended in a culture medium and deprived of the feeder cell layer. Conditions are then sufficient for the ES cells to survive but not for their self-renewal and proliferation. The cells then form spontaneously into cellular clusters called "embryoid bodies" which acquire a hollow structure resembling that of blastocysts from which differentiated cells characteristic of the three embryonic layers are detached. Some cellular types form spontaneously: this is the case of hæmatopoietic cells and of cardiomyocytes which, after 14 days, when in contact with the endodermic type cells, appear and contract with the pulsatility which is characteristic of the human species[21]. Neural precursors, the neurospheres, can also be identified and they can be isolated and differentiated *in vitro* into neurons, astrocytes and oligodendocytes[22].

Programming this differentiation of stem cells is an important milestone for therapeutic uses. Certain growth factors can control the differentiation of ES cells in a reproducible manner. It is also possible to select certain cellular types for specific molecular marking, isolation and the development of pure cultures.

Origin

Although the provenance of ES cells is invariably the blastocyst ICM, there are multiple starting points and origins for the blastocyst, among which the main sources are:

- the most obvious are supernumerary embryos resulting from IVF (*in vitro* fertilisation) or ICSI (intracytoplasmic sperm injection), frozen embryos for which a parental project no longer applies. It will now be possible in France to use these embryos with the consent of the parental couple and as part of a research programme controlled by the *Agence de Biomédecine*. Every year, 40 to 45,000 embryos are frozen, most of which are thawed for later use as part of the original parental project. As of December 31, 2001, there were 96,584 cryopreserved embryos stored in liquid nitrogen containers in ART (Assisted Reproduction Technology) centres. Some 60,000 of those embryos were still involved in a parental project and 15,000 were no longer claimed by couples who were not responding to reminders or could not be contacted. That left 23,000 embryos for which the future potentially held the possibility of cessation of conservation, donation to another sterile couple (embryo hosting) or donation for research. The ART centres find that this latter option seems only to be chosen for 20% only of the embryos for whom there is no further parental project. Such evaluations may of course vary as time goes by and exciting research programmes are developed, but this represents at this time, 4,600 embryos of which 75% survive thawing, i.e. potentially 3,500 embryos for "French" research. As of now, the various groups attempting to derive stable ES cell lines using supernumerary human embryos, claim a success rate of approximately 20%, which will probably be improved with time. Therefore, existing frozen supernumerary embryos could be the origin of several hundred cell lines.
- embryos derived from ART with mediocre morphological and kinetic qualities are considered to be incapable of implantation; they are more often than "normal" embryos (>80%) the carriers of chromosomal anomalies. They are therefore eliminated. They represent some 100,000 human embryos conceived in vitro in France every year. And yet, in a small number of cases and despite a discouraging appearance, some of these embryos are still capable of development. Recently, two teams of researchers have published the results of tests to grow these "poor quality" embryos: 15% of them were

[21] Mummery et al, 2005.
[22] Reubinoff et al 2001.

still able to develop into blastocysts. It is true that these blastocysts were not of the best quality either, but in 10% of cases they were the origin of stable cell lines (pluripotence maintained for over 12 months, with a normal karyotype[23]. It is difficult to say whether these embryos could have, after transfer in utero, given birth to normal children since at this time it is impossible to distinguish with any certainty those that would not have developed. This would add up to 1500 ES cell lines that could be grown every year.

One of the major problems in cell therapy is the immune tolerance of the cells. Although animal experiments seem to show that embryonic cell immunogenicity is low, in order to avoid having to use immunosuppressive treatment, it would be helpful to benefit from the availability of cell banks of various HLA types, which requires a large number of cell lines and a large number of embryos. For that reason it would be worthwhile to diversify the source of available human embryos. Another problem, highlighted by recent research, is also inherent to all sources of embryonic stem cells. If cell lines are derived from blastocysts which were not implanted because they were not viable, would the cells in question have good therapeutic value and be biologically safe to use?

- In the United States human embryos have been created using oocytes and sperm from young and fertile donors to isolate ES cells[24] (in France, this process is prohibited).
- Other avenues have been explored which could not be exploited for cellular therapy but illustrate the diversity of ongoing research: blastocysts derived from parthenogenetic zygotes following spontaneous[25] or inducted oocyte[26] activation; blastocysts derived from the chimeric aggregation of blastomeres from morphologically abnormal embryos; and particularly embryos carrying a genetic anomaly detected by preimplantation diagnosis as the origin of cell lines available for research[27].

Advantages and drawbacks

Among the advantages of ES cells, three are particularly noteworthy: 1) pluripotence making it theoretically possible to derive the majority of the various differentiated cellular types; 2) the possibility of getting these cells to proliferate in culture and thereby amplify the number of cells available for therapy and; 3) the capacity to maintain these cells and freeze them in the form of stable undifferentiated cell lines.

Among their drawbacks, their embryonic origin, their antigenicity, their capacity to form tumours *in vivo* if their prior differentiation is not assured, are so many limiting factors.

2) Embryonic stem cells derived from nuclear transfer (also called therapeutic cloning)

Before any discussion of this theme, it must be emphasised that nuclear transfer is prohibited in France and in a majority of countries in the Western world at this time. We are discussing the subject here because nuclear transfer can be one way of obtaining embryonic stem cells; under no circumstances would cell lines derived from nuclear transfer be put in the same category as "natural" stem cells. As a consequence, the mention of the subject in this Opinion is in no way to be understood as either approval or disapproval by CCNE of nuclear transfer.

Background

[23] Chen et al, 2005; Mitalipova M, 2003.
[24] Lanzendorf, 2001.
[25] Suss-Toby, 2004.
[26] Lin, 2003
[27] Pickering, 2003.

Recently, immune deficient mice (Rideout, 2002) or with Parkinson's (Barberi, 2003) were successfully treated by the transplant of autologous embryonic stem cells derived from blastocysts obtained by somatic cell nuclear transfer (SCNT). This combination of the technology that produced Dolly and the one which is at the origin of ES cells solves the problem of the immunogenecity of embryonic stem cells, using a procedure which is commonly called "therapeutic cloning". At this time, despite some premature attention-catching announcements, the nuclear transfer method for humans is not mature.

Advantages and drawbacks

Among the advantages, the autologous nature of the ntES cells must be emphasised. Such stem cells would be particularly well suited to cell therapy because of the absence of the risk of rejection.

Among the drawbacks, the most frequently raised problem is the ethical risk involved in the technical proximity of "therapeutic" or "scientific" cloning and reproductive cloning. Harvesting the number of oocytes required to arrive at large scale cellular therapy seems hardly compatible with respect for women's health and free will.

3) Embryonic Carcinoma stem cells (EC cells)

These cells have very similar properties to those of ES cells and differentiated neural cells derived from EC cells have been used, despite their tumoral nature in a Phase 1 trial on 11 stroke victims, without any apparent side effects but without any great benefit[28].

4) Fœtal stem cells

These cells are derived from fœtal tissues from aborted fœtuses (5 to 9 weeks). They are abundant and of different types:

Somatic fœtal cells: fœtal tissues contain multipotent stem cells; stem cells derived from neural tissue have already been used in the treatment of neurodegenerative diseases such as Parkinson's and Huntington's diseases and the allograft of fœtal neurons has proved to be effective with lasting benefit since the grafted cells are still functional years later as has been verified (with Positron Emission Tomography/PET scans) in patients treated in Sweden. The technique however requires a considerable amount of fœtal tissue and logistic constraints limit development.

EG germ cells: In 1988, Shamblott et al showed that it was possible to grow pluripotent cells, very similar to ES cells, from primordial germ cells present in the genital crest of aborted fœtuses. Such cells however are difficult to isolate and culture and only the Shamblott group has managed to do so.

Hæmatopoietic stem cells (HSC) derived from cord blood: in the first few hours after birth, the HSC in fœtal circulation migrate to the bone marrow where they form the progenitors of all the blood cells. Also found in the 100 ml of blood contained in the cord and the placenta, which are eliminated after delivery, are HSCs in sufficient quantities to repopulate a child's bone marrow. Such HSCs are obviously perfectly compatible with the donor but also with siblings or other relatives (see Opinion N° 74 dated December 12, 2003: "Umbilical Cord Blood Banks for Autologous use or for Research".)

5. Adult stem cells

Background:

Blood cells and those of the epidermis and intestine are in constant renewal throughout life, which is evidence of the existence of active stem cells. The stem cells of blood, bone

[28] Kondziolka, 2000.

marrow and the skin are easily accessible and already in therapeutic use. In recent years, there has been evidence that other organ or adult tissues (brain, blood vessels, muscles, digestive epithelium, dental pulp, retina, liver and pancreas) contain stem cells.

Adult stem cells from a donor organ

Such cells are capable of self renewal and capable of differentiating into the specialised cell types of the tissue they come from. They could therefore contribute to the replacement of cells that have died a natural death or after a lesion. However, they do not seem to be very active if at all and do not seem to mobilise very much spontaneously if at all to repair extensive lesions or dysfunctions.

Potentially pluripotent adult stem cells

It was a long held belief that adult stem cells could only form the cellular types of the organs they were located in. Recently however, it has been demonstrated that they could differentiate into cells derived from the same embryonic layer: bone marrow cells becoming muscle cells from the same mesodermic cell line.

Transdifferentiation also seems possible: bone marrow cells transforming into hepatocytes. But it was also demonstrated that this event was secondary to a cellular fusion process. The picture is not yet entirely clear as regards the reality of such events nor whether they occur spontaneously or after *in vitro* induction. Several observations on the beneficiaries of bone marrow donation, when the donor was of the opposite sex, plead in favour of the reality of the phenomenon. Several years after the graft, autopsy reveals myoblasts and epithelial cells completely integrated in the beneficiary's muscular tissue but which originated in the donor. Human mesenchymalatous stem cells derived from bone marrow do seem to be gifted with multipotentiality[29]. There have been reports that there are, in particular in human bone marrow, stem cells capable of giving birth to cells from all three embryonic layers, but this is still very controversial. Although they may be few in number, if their existence were to be confirmed, these cells would be accessible and therefore could become good candidates for cellular therapy.

Advantages and drawbacks:

A patient's stem cells could be used for self-repair while avoiding any immunological risks and ethical controversy. Such cells would ideal for regenerative medicine.

The drawbacks reside essentially in the feasibility of this approach. Compared to embryonic stem cells, adult stem cells are very scarce, their proliferation potential diminishes with donor age, they are more difficult to maintain undifferentiated in culture and confirmed, but restricted, plasticity limits their capacity to differentiate into specific cell types.

[29] Jiang, 2002.

ANNEX II

POTENTIAL USES OF STEM CELLS

"Adult" stem cells and fœtal cells

Adult stem cells are used for cellular therapy, that is using cells whose properties or characteristics have been modified after they were harvested from a living individual. The prototype of organ stem cells of the adult kind are the hæmatopoietic stem cells (derived from bone marrow, mobilised in the blood, or from cord blood). They have been in use for about forty years. Stem cells from the skin, cartilage and bones are now beginning to be used for therapeutic purposes.

The possibility of extending the therapeutic use of stem cells from various organs could give rise to the development of regenerative therapy. It would be possible to repair cell losses observed in the nervous system with Parkinson's disease, or in the pancreas in the various forms of diabetes, in the myocardium after an infarct, or in tissue development disorders such as myopathies.

The donor's organ stem cells could conceivably be used autologously (donor and patient one and the same) or allogenically (donor and patient not the same person). To enable the transfer of cells from one person to another, cell banks could be set up which would solve the problem of tissular HLA group compatibility (as is already the case for cord blood cell banks, see Opinon n° 74 dated December 12, 2002 on "Umbilical Cord Blood Banks for Autologous use or for Research".).

Adult stem cells can be modified for therapeutic purposes by gene transfer. This has already been successful with medullar cells in various forms of immune deficit and could be considered in the case for example of cystic fibrosis or certain genetic liver diseases. More recently, multipotent adult stem cells, i.e. capable of giving rise to various types of tissue, and stem cells capable of plasticity and therefore of differentiating into a different tissue than those that stem cell differentiates into *in vivo*, have been the subject of study. Such cells could also be used in therapy, either autologously or allogenically.

However, the use of adult stem cells raise a number of scientific problems which have not been solved as yet.

Some organ stem cells, other than hæmatopoietic stem cells, for instance skin, cartilage and bone stem cells which would seem to be present in each of these organs, are only present in very small quantities. They are therefore very difficult to obtain. Also, amplification and differentiation of these cells (and decoupling conditions) are not perfectly controlled at this time.

For multipotent stem cells, much remains to be done as regards their characterisation, the study of their potential and repeatability of the data. The conditions in which such cells could be amplified to enable therapeutic uses remain to be defined as well as the conditions in which it might be possible to obtain, repeatedly, differentiation into a given tissue. The very notion of tissular plasticity is disputed and requires further cognitive research activity before any therapeutic development is attempted.

Comparable therapeutic prospects are conceivable for stem cells derived from fœtal tissue. The potential existence of pluripotent stem cells in fœtal organs is presently being explored.

Embryonic stem cells

The multipotent capacity of embryonic stem cells seems encouraging for their use in regenerative therapy. However, two other potential uses should be considered:

- obtaining embryonic stem cell lines capable of differentiation into other tissues, for the purpose of pharmacological and pharmacogenetic study;

- obtaining pathological embryonic stem cell lines from pathological embryos originating in preimplantation diagnosis (see Opinion n° 72 dated July 4, 2002: "Reflections Concerning an Extension of Preimplantation Genetic Diagnosis".). Cell lines such as these could be the object of physiopathological studies and possibly of therapeutic testing for the genetic disease concerned.

In scientific terms, embryonic stem cells are an essential element for studying developmental biology.

The questions raised by the study of these cells are numerous: detailed knowledge of the molecular processes involved in the preservation of self-renewal capacity, detailed analysis of the molecular programmes for cellular differentiation, capacity to control *in vitro* cellular differentiation conditions (in particular as regards the use of cytokines or stromal cells) and completely safe optimal culture conditions.

Apart from the difficulties connected to insufficient knowledge of embryonic stem cells, the potential limits of use of such cells for therapeutic purposes must also be mentioned:

- limitations in the precise control of the differentiation programme in order to obtain the required cell type (for example: a certain type of neurons located in a certain type of basal ganglia)
- risk of cancer development if cells were not completely differentiated *in vitro*
- and above all the inherent risk of incompatibility within the major histocompatibility complex between donor and potential beneficiary. The risk of rejection must be further studied to ensure that it can be avoided. Here again, the development of embryonic stem cell banks expressing various combinations of HLA tissue groups could be considered following the model adopted for cord blood cells.

Nuclear transfer

Nuclear transfer is prohibited in France at this time. The following is therefore purely hypothetical.

Obtaining embryonic stem cells by nuclear transfer could offer glimpses of potential uses for regenerative therapy. However, it is infinitely probable that this technique will first be used to obtain cell lines derived from pathological material so as to enable extremely valuable physiopathological work to be done (for instance, obtaining precursor neuron cells from nuclei derived from a somatic cell in a patient suffering from a serious developmental disorder of the central nervous system). Such cells could also be used for therapeutic tests *in vitro*, and in the longer term perhaps also for gene transfer.

Scientific problems are legion among which, first and foremost, controlling the nuclear reprogramming process.

The methodology of nuclear transfer encompasses of course all the difficulties inherent in the development of the use of embryonic stem cells with perhaps the exception, as regards therapeutic applications, of incompatibility and therefore the risk of immunological rejection, since the genetic material of such cells would have the patient himself as its source.

Cell lines not derived from stem cells

Finally, it must also be said that cellular therapies involving the injection of T lymphocytes obtained from the donors' blood and selected in vitro on the basis of their specificity (antiviral, antitumoral) are in the process of development. It may be surmised that in the future other cell lines (non stem cells) could also be used for cellular therapy (other lymphocyte populations or dendritic cells).

ANNEX III

The patentability of stem cells: the *WiCell* example

As an illustration of this issue, this is an example of patent transfer to a not-for-profit foundation for the development of research on embryonic stem cells. This example shows how a foundation and a company set up conditions ensuring both protection and absence of payment for the use of such stem cells.

Following work on obtaining human embryonic stem cells, a patent was granted to the principal author, James Thomson from the University of Wisconsin. The patent covered both the method used to isolate embryonic stem cells (process patent) and the five stem cell lines (product patent[30]). In compliance with the University of Wisconsin's own regulations, James Thomson transferred the patent to his University's supporting organisation, the Wisconsin Alumni Research Foundation (WARF) — a non profit foundation which negotiates and establishes licensing agreements. In particular WARF, which owns the patent, includes in all its contracts a clause which stipulates unimpeded and free-of-charge distribution of patented material to be used for research.

Furthermore, WARF has created another non-profit organisation, the WiCell Research Institute (headed by James Thomson) to manage the conservation, multiplication and distribution of these stem cells which requires constant and intensive attention.

Stem cells are distributed free of charge to scientists requesting them under the following conditions:

1. WiCell retain ownership of the cells made available to researchers.
2. These cells must not be used for diagnostic or therapeutic purposes; their use is solely confined to education and non commercial research.
3. Use of the cells must comply with applicable rules, regulations and guidelines.
   In particular, it is not permitted to:
   - mix the material with an intact human or non-human embryo;
   - implant these cells in a uterus;
   - to attempt to make whole embryos derived from the cells.
4. Should a scientific discovery based on this material be usable for commercial purposes, a separate written agreement will be arrived at between WiCell and the scientist concerned to define and regulate the commercial outcome of the discovery.
5. WiCell may demand payment for the preparation and distribution of stem cells to recipients.

In France and the rest of Europe, legislation differs in that there is exemption at the outset in favour of research, which means that research may be conducted on elements or products covered by a patent on the condition that such research is not associated with any commercial exploitation. It is therefore unnecessary to refer specifically to exemptions for research in technology transfer contracts.

[30] EGE Auditions, November 20, 2001

ANNEX IV

OPINION OF THE EUROPEAN GROUP ON ETHICS OF 7 MAY, 2002 ON THE PATENTABILITY OF STEM CELLS

According to the EGE Opinion[31] dated May 7, 2002, there have been over 2000 patent applications involving human and non human stem cells, of which one quarter refer to embryonic stem cells.

These patent applications bear on:

- either processes: processes for isolating stem cells from embryos or tissues; processes for enrichment of stem cells in mixtures of cells; processes for culturing stem cells; processes for genetically modifying stem cells; processes for inducing the differentiation of stem cells; processes for inducing adult stem cells to undergo 'retrodifferentiation' or 'transdifferentiation'; processes for transforming somatic cells into stem cells,
- or products: involving stem cells, stem cell lines, differentiated stem cells and genetically modified stem cells.

As regards the patentability of stem cells, the European Directive 98/44/EC of 6 July, 1998 and its transposition to the French laws on Bioethics in 2004 are very explicit[32].

EGE's Opinion n° 16 concludes that it would not be advisable to prohibit any patenting of stem cells or stem cell lines as it would, according to that Opinion, be contrary to public interest in general and patients' interests in particular.

The Opinion also recommends that a distinction be made according to the nature of the material: isolated stem cells or stem cell lines that have not been modified do not as a product fulfil the legal requirements to be seen as patentable. Inversely, stem cell lines which have been modified by *in vitro* treatments or genetically modified so that they have acquired characteristics for specific applications would seem to fulfil the legal requirements for patentability. *In fine*, the Opinion insisted on the need for Patent Offices to avoid granting too broad patents for stem cell lines that could impair further research and development.

As a result, stem cells of adult origin could be patented following the status conferred on cell lines:

- if they are products of the human body which have simply been detached and have undergone no transformation, they do not fulfil the legal requirements to be seen as patentable,
- if they are products derived from the human body, that is cell lines derived from isolated stem cells, obtained by a technical process in vitro, that could not be viewed as natural stem cell lines, they could be patented.

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[31] Opinion n°16 of the European Group on Ethics in Science and New Technologies (EGE) dated May 7, 2002: Ethical Aspects of Patenting Inventions Involving Human Stem Cells.

[32] " Art. L.611-17: (code de la propriété intellectuelle - code of intellectual property): are not patentable inventions whose commercial exploitation would be contrary to the dignity of human beings, public order and morality..."

"Art. L.611-18: the human body, at various stages of its constitution and development, as well as the simple discovery of one of its elements, including a total or partial gene sequence, cannot be taken as patentable inventions. Only an invention involving the technical application of a function or element of the human body can be patent-protected. Such protection only covers the element of the human body in so far as this is necessary to the realisation and exploitation of that particular application. In particular, are not patentable: a) processes for the cloning of human beings, b) processes for the modification of the genetic identity of human beings, c) the use of human embryos for industrial or commercial purposes, d) total or partial gene sequences as such".

Product patenting for stem cells would therefore be acceptable, according to the directive, on the condition that such cells are viewed as being "processed and transformed". Similarly, process patents for obtaining cellular therapy products could be granted if the technical conditions are fulfilled.

However, it is to be expected that the cell lines themselves cease to fulfil patentability criteria for insufficient novelty, invention or industrial application (following chromosomal rearrangement, they could become dangerous and ineffective), but that is a technical problem to be solved by Patent Offices on the basis of applicable rules.

The European Group on Ethics' Opinion n° 16[33] also underlines that those who oppose embryo research will be in principle opposed to any kind of patentability. But those who accept embryo research may be reluctant to accept the notion of patenting embryonic stem cells. Others, considering the expected medical benefits, would consider patentability as acceptable.

Article 6 of directive 98/44 provides for a certain number of exclusions from patentability for reasons of 'ordre public' and morality and in particular specifies that the use of embryos for industrial or commercial purposes is not patentable. But paragraph 42 of the Preamble adds that the exclusion does not concern inventions relating to human embryos for therapeutic or diagnostic purposes.

Although the industrial or commercial use of human embryos[34] is excluded from patentability by virtue of article 6 of the directive, this prohibition does not apply to embryonic stem cell lines which can no longer be considered embryos. Such cell lines can therefore be process- or product-patented[35].

The Opinion also specifies that this article does not give any definition of embryos concerned by the exclusion so that certain embryos could be exempt: these would be non viable (that cannot lead to any birth) embryos such as those created by parthogenesis. However, a limitation arising out of article 6 paragraph 2 a would seem to apply: are not patentable "the proceeds of cloning of human beings", clause according to which, notes Opinion n° 16, should be excluded from patentability the proceeds of creation of human embryos by cloning in order to obtain stem cells.

Inversely, the question of consent for later exploitation by a patent is not to be found in legal patent regulations and does not appear in the articles of the directive. Only paragraph 26 of the Preamble mentions such consent and recommends its use.

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[33] Previously quoted, note 48

[34] EGE's Opinion n°15 of November 14, 2000, "Ethical Aspects of Human Stem Cell Research and Use" recommended that steps be taken to prevent the commercialisation of human embryos of tissues from dead fœtuses.

[35] To that effect, TA Paris, January 21 2003 confirmed on appeal by decision of May 9, 2005.