

OPINION N° 112

**Ethical reflection concerning research on human embryonic cells and
on human embryos *in vitro***

Members of the Working Group:

Jean-Claude Ameisen (rapporteur)

Ali Benmakhlouf

Claude Burlet

Alain Cordier (rapporteur)

Patrick Gaudray

Xavier Lacroix

Claude Sureau

Bertrand Weil

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Ethical implications of respect for the beginning of life.

This reflection on the issue of research using human embryonic cells and, separately, on research using human embryos, constitutes a contribution of the National Consultative Ethics Committee for Health and Life Sciences to reflections prior to a re-examination of the law on bioethics dated August 6th, 2004.

Putting the issues in context.

A. brief history of Assisted Reproductive Technology (ART): from *in vitro* fertilisation to the issue of destroying spare embryos.

In vitro fertilisation (IVF), developed as part of Assisted Reproductive Technology (ART) in order to alleviate the distress caused by infertility, rendered dissociation between procreation and sexuality possible and led to the birth in 1978 in the United Kingdom of the first "test tube baby", Louise Brown, and in 1982 in France to the birth of Amandine.

It was precisely these ethical issues, which arose following the profound changes due to advances in ART in France that led to the creation of CCNE in 1983.

The following year, this dissociation in time acquired an entirely different dimension with the development of *in vitro* embryo freezing (or cryopreservation) which made it possible to defer transferring the embryo to the body of the mother, thus eliminating any *a priori* notion of a maximum time limit between the moment of fertilisation and the moment when pregnancy begins.

Since then, over four million ART births have occurred worldwide, some 200,000 of which in France.

Such changes could not but have a major influence on perceptions.

Not only were perceptions concerning embryos radically changed, but also those concerning *parental projects* which took on a new dimension. A prior parental project now needed to be formulated for the possibility and reality of IVF to apply, that is through embryo conception outside the mother's body.

In tune with the new importance acquired by *parental projects* emerged a new form of medical and social responsibility concerning the embryo's fate before transfer to the mother's body.

In this radically new context for the start of a human life, emerged the new issue of the future of the *in vitro* embryos if they were not to be transferred to their mothers' bodies.

Today, there are at least three sets of circumstances leading to a medical decision not to transfer an embryo created through ART *in vitro* in the context of a parental project:

1. when the presence of a major defect or the fact that an embryo has ceased to develop *in vitro* is clearly visible before transfer to the mother;
2. when preimplantation genetic diagnosis (PGD) reveals that an embryo is carrying the genetic sequence involved in a particularly severe inherited disorder, incurable at the time of

diagnosis, the genetic sequence in question being the one which initially motivated the PGD¹ procedure.

In both cases, the human embryo is destroyed.

3. There is a third set of very different circumstances in which embryos created *in vitro* are not transferred: in this case the decision is taken to cryopreserve the embryos so that they may be transferred later in the event of the first attempt at transfer being unsuccessful, or if the couple wish to have another child at a later date without having to undergo over again hormonal hyperstimulation and oocyte collection procedures, thus avoiding additional risk to the mother's health. **They then become so-called *spare or supernumerary embryos*, awaiting later transfer.**

But if, at some later time, the parents of these cryopreserved supernumerary embryos cease to have plans involving them, the embryos are no longer simply in *excess* in the context of the ART procedure involved: they become **in excess — surplus to requirements — to the very parental project that was at the origin of their conception. **This is the situation which led to the issue of *ceasing to keep them*, i.e. the issue of *their destruction*.****

B. From the issue of destroying spare human embryos to the issue of research on embryonic cells and on human embryos *in vitro*.

The solutions provided by ART (by the creation and cryopreservation of spare embryos) and preimplantation genetic diagnosis to **medical ethics issues** (see above) **have brought in their wake another kind of ethical problem**, that of the possibility that embryos could **cease to be preserved**, and therefore that embryos *in vitro* could be **destroyed**, either in the course of PGD, or when spare human embryos are no longer part of a parental project. Furthermore, the problem has never ceased to grow in importance along with the development of the use and practice of ART.

And so, medical ethics issues, **dating back to over twenty five years ago**, have led to the **decision of destroying human embryos** in an ART context, **independently of any consideration of possible research on embryos or embryonic cells.**

It was only much more recently, a little over 10 years ago, that embryonic human stem cells were identified and isolated and **suddenly became of major scientific interest** in a large number of biomedical research domains, which led to considering the possibility of human embryos as a potential source of stem cells for biomedical research and other medical purposes.

C. Positions which are *a priori* irreconcilable.

1. Beyond divergences: a position in common?

We are not intending to give an exhaustive description of the very great diversity of opinions regarding the manner in which human embryos *in vitro* should be treated, nor of the various legislative interpretations of such treatment in different countries around the world. Rather, we seek to highlight both the essential differences which oppose them, frequently very

¹See CCNE's *Opinion N° 107*, October 15, 2009 on ethical issues in connection with antenatal diagnosis: Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)

radically, in ethical terms and, transcending these differences, to discover possible points of convergence.

In some opinions, the very creation of an embryo *in vitro* as part of an ART procedure should be banned and the wish to have children should only be fulfilled if it can be achieved without IVF.

But with the exception of this view, **there is at least one point — and it is all too infrequently underlined — common to all the radically different opinions on how human embryos *in vitro* should be treated: the embryo's integrity must not be breached as long as it is still included in the parental project which was the cause of its creation.**

In other words, **there is one true interdict, shared by everyone: the integrity of embryos *in vitro* cannot be jeopardized as long as they are included in the concerned couple's plans to have a child.**

This common stance of respect for human embryos *in vitro*, as long as a parental project persists, is held by all, including those who consider that a parental project cannot in itself be the only reason for respecting human embryos.

This common stance also has a characteristic which deserves to be underlined: both respect and interdiction are related to the preservation of a human bond.

This human bond between the future parents and their future child, is pre-existent to the creation of an embryo *in vitro*. It is the very condition for its creation by ART.

It is because of the existence and persistence of this **human bond** that an embryo *in vitro*, already a "potential human being", becomes an incipient² "potential human being".

Nor is it any longer biological development which determines — and determines alone — the future of an embryo; it is the human bond of which the embryo is a part. To become one with human lineage is not defined in purely biological terms; being part of a human relationship is the determining factor.

But the creation of excess human embryos opens up the possibility of this bond being broken. Excess embryos are no longer the sole purpose of the bond, in other words, no longer future children. The embryo becomes in fact one of the means to that end, no longer *incipient*, but *in waiting*, while another "potential human being" is the present tense of the bond, the reality of what is to come.

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It is with explicit reference to this human bond that the *Avis citoyen du Panel de Marseille* used the term "personne humaine en devenir" (incipient human being) to characterise an embryo which is still included in a parental project at the *Etats Généraux de la Bioéthique* in 2009.

2. When the embryo *in vitro* is no longer — or never was — part of a parental project: radically different positions.

There is a radical opposition between the various opinions on how embryos should be considered. These differences are founded, in particular, on philosophical or religious positions which are difficult to reconcile. **The various positions can be summed up, probably in an over-simplification, as follows:**

- For some, a human embryo can only be created in the context of a parental project, but in strict subordination to respect for the future of the embryo. Once fertilisation has taken place, the dignity of the human being is already fully present: *all is already* there (as regards dignity and respect)³, even if this *all* is only present in the form of a beginning, a development, an incipient future.

In this representation, the **embryo *in vitro* is already entirely at one with the "human lineage"** insofar as the embryo is the starting point in a developing human continuum. The embryo is where human life began, and this life once begun is already seen not so much as a *potential person* as an *incipient person*.

Albeit very important, the conditions of the embryo's future — implantation, relationship with the mother's body, epigenesis, parental project — do not condition the embryo's being. At the precise time that an egg is fertilised by a sperm cell, a new life begins which may, in the course of a continuous process, develop into a person. The continuum has precedence over all the "stages" which may be singled out in the process.

Even though the embryo may not as yet be seen as a person, its dignity is *already* equal to that of a person and the respect that is owed to it is therefore identical to the dignity owed to a person.

For this reason, a fundamental prohibition is demanded for any breach of the embryo's integrity and, to achieve this, in particular a ban on the production of spare embryos and their cryopreservation in the course of ART.

- For others, and this was the case in particular for the *États Généraux de la Bioéthique* in 2009 (Estates General on Bioethics, 2009), embryos can only be created in the context of a parental project, **but respect for the embryos' future is entirely subordinate to respect for the future of the parental project.**

Respect for the embryo *in vitro* does not correspond to a point in time — to any specific stage — of its development, nor to the moment when an actual link between the embryo and its mother is established, that is the time of implantation, but rather to an early representation of this link in the future and to the embryo's enrolment in this prefiguration of the future parental

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It is worthy of note that, in biological terms, the demarcation point of fertilisation, between the *nothing yet* status and the *already everything* status, is in fact a continuum and that the dividing line becomes much more visible with hindsight. About 24 hours elapse between the time when the spermatozoon penetrates the egg and the moment when its chromosomes have merged with the oocyte's, leading to the creation of the embryo's chromosomes and its first cell.

link. If the parental project itself becomes redundant, then retrospectively the protection granted to the embryo *in vitro* against a breach of integrity is also lost⁴.

- **Yet other opinion groups consider** that respect for embryos is solely conditioned by their inclusion in a parental project and that **the absence of any such parental intention therefore authorises their creation *in vitro* for research purposes**, independently of any ART procedure.

The ethical issue arising in that situation is the maximum amount of time allowed before destruction of the embryo. This would be a boundary, a limit corresponding to a specific stage in the development of the embryo *in vitro*.

There are several different perceptions regarding such a boundary.

- For some, the dividing line is the stage of biological development which corresponds to the possibility of implanting in the mother's uterus. This stage occurs on the 7th day of embryo *in vitro* development. An embryo created for research should therefore be destroyed before it reaches that stage^{5, 6}.

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Report by the *États Généraux de la Bioéthique. Annex 9. Contributions from Regional Forums. Citizen opinion given by the Marseilles panel. Estates General on Bioethics. Chapter I. Stem cells and research on embryos of the Citizen Opinion begins as follows:*

"We, the citizens, consider that a protective status should be granted to embryos, in the framework of a parental project, based on the principle of non instrumentalisation of the unborn child. Embryos should have the status of an incipient person only when they are enrolled in a parental project. It is this project which confers a status on embryos and therefore defines them. The absence of a parental project cancels the status given to them.

If and when the parental project becomes redundant, as may be the case for excess embryos, we are in favour of using the embryos for research, subject to explicit agreement from those who conceived them.

Conversely, we are opposed to any form of research on embryos intended for implantation, since they are part of a parental project."

As regards the length of time excess embryos should be kept for, the Opinion continues:

"We consider that the five year time period provided for the conservation of excess embryos that are no longer included in a parental project is too lengthy. We would recommend that this time should be reduced to one year, with the possibility of a single one year renewal. No response from parents by the end of this period signifies the end of the parental project. We would also consider it highly desirable that detailed information be given at this time to intentional parents and that they should be asked at the outset to take a decision on what should be done with superfluous embryos should they not respond to enquiries at a later date (destroyed, given to another couple or donated for research purposes). In this way, the point could be made more clearly that the intended parents, and not the doctors, would bear the responsibility for the possible destruction of the embryos. It would also be appropriate at that point to explain more fully the usefulness of donating embryos for research."

This recommendation for shortening the time of conservation of excess embryos to one year with the option of a renewal for one more year, had already been formulated, almost 25 years ago, by CCNE in Opinion N° 8, December 15, 1986 on *Research and use of in-vitro human embryos for scientific and medical purposes*.

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It was in this context that the proposal was made to give the name of *pre-embryo* to the embryo *in vitro* as long as it has not reached the stage of development when implantation becomes possible. The creation of embryos *in vitro* for the sole purpose of destruction and research is seen as not raising any other ethical issue than the one mentioned above, i.e. collecting oocytes for research (see above), provided the embryo *in vitro* is destroyed before the 7th day following its creation.

- For others again, the radical frontier appears later in the process, i.e. on the 14th day of development *in vitro* with the emergence of the first differentiated cells giving rise to the nervous system⁷.

3. “Seeking the lesser evil”.

It is perhaps starting from this sole point in common between two positions which seem *a priori* mutually exclusive — respect for the embryo *in vitro* included in a human connection, a parental project, the very condition for its future — that the ethical issue of a common mutually acceptable approach, regarding the embryo, may be based.

This concept of a boundary and of the absence of any ethical problem is shared by other opinion groups as regards the method used to create *in vitro* embryos when there is no fertilisation process, such as *transferring the nucleus* of a somatic cell to the cytoplasm of an oocyte from which the nucleus was removed (or *cloning for scientific purposes*), or again the formation of *cybrids* (transferring the nucleus of a human cell to an animal cell from which the nucleus has been removed). In such cases, some people are of the opinion that not only is there no ethical issue because these are pre-embryos, but that there is even less of a problem since the *pre-embryo is artificial* and the decision in advance was that it would never be implanted, whatever the circumstances.

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Reading CCNE's Opinion N° 67, dated January 18, 2001, on the *Preliminary draft revision of the laws on bioethics*, shows just how much this concept of a boundary has resonance, and how the refusal to validate one form of a radical boundary, because of an apparent rejection of this very principle, can lead to validating another form of boundary — just as radical as the first kind. In the chapter on the *Nature of the Embryo*, (dealing with the subject of creation of embryos for the purpose of research by nuclear replacement, i.e. “so-called therapeutic cloning”), “CCNE stresses the fact - in its opinion a very positive one - that the preliminary draft law designates all three kinds of embryos by the expression “human embryo”, which was not a foregone conclusion for two reasons. Firstly, if one considers the procedure consisting in transferring a cell nucleus into an enucleated oocyte, the resulting product must needs be a human embryo by its very nature. To deny this would mean, were the prohibition disregarded, denying in advance human status to the child produced. Such a dividing line must not therefore be drawn between an IVF embryo and an embryo [created by nuclear replacement for research], even though it is clear that their origins - sexual reproduction in one case, and asexual in the other - introduce an essential difference which is due in part to the nature of the project which originated them and which justifies the radical difference in treatment introduced by the law.”

CCNE concluded with a “firm reminder of the principle that creation of human embryos for the purpose of research is prohibited.”

But “On the subject of therapeutic cloning, however, opinions differ. There is general agreement that this subject raises extremely difficult ethical issues, but members of CCNE are divided, depending on their vision of the world and of the future, between two positions which have been outlined above. There is a majority in favour of the second of these positions, i.e. the one which favours controlled authorisation to engage in 'therapeutic' cloning.

In other words, the process which consists in first rejecting a radical boundary, then adopting another boundary, just as radical but of a different kind, leads to paradoxical proposals, the apparently contradictory nature of which is not discussed: on the one hand, the embryo created by nuclear replacement is a “human embryo”; on the other, “the creation of human embryos for the purpose of research is prohibited”; and yet, a majority in CCNE is in favour of authorising the creation of human embryos by nuclear replacement for research purposes!

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This is the case in the U.K. (see below, Chapter III of the Consideration of the issues). Previously, in the first two weeks, the embryo *in vitro* is as *nothing* (in terms of dignity and respect). The creation of embryos for the sole purpose of research and destruction, be it by fertilisation, *nuclear replacement*, or the creation of *cybrids*, does not raise, as in the previous configuration, any ethical issue as long as the embryo created *in vitro*

In this context, attaching exclusive importance to the parental project, to a couple's intention of giving birth to a child, could lead to no longer ascribing any importance at all to the creation and future of spare embryos. Conversely, granting exclusive importance to the future of spare embryos could lead to no longer ascribing importance to the human connection which is the very reason for the creation of embryos *in vitro*, that is the relationship between the partners and the projection of that relationship in a parental project, seeking for a bond in the couple's future with their future child.

It is the existence of this **human bond**, this inclusion in a parental project, which, as the Estates General on Bioethics stated, turns the **“potential human being”** that an embryo *in vitro* is for CCNE, into an **“incipient” potential human being**.

As CCNE remarked nearly twenty-five years ago: **“...although it cannot be demonstrated, the belief that a human life cannot be entirely controlled because it is not a manufactured product is a guarantee of our liberty and dignity⁸.”**

CCNE's position has always (or nearly always⁹) consisted in not drawing a boundary which would lead to an all or nothing approach to respect for the embryo, and **in considering the “issue of the exact nature of the embryo” to be an enigma**: “It would be just as excessive to consider the pre-implantation embryo as simply a bundle of cells of human origin, as to consider it sacred because it is a potential human person. The notion of "on-going embryonic process" could perhaps represent the *enigma* (italics added) which veils the exact nature of the embryo in the very first moments of life. Be that as it may, and precisely because of this *enigma* (italics added), the Committee declares its attachment to the view that the human embryo must, as soon as it is formed, receive the respect owed to its status¹⁰”.

If the embryo *in vitro*, as soon as it is created, is considered to be a person already, the ethical issue of the creation of spare embryos and therefore of their possible destruction, does not even arise: creating spare embryos is unacceptable.

If, on the contrary, the embryo *in vitro* is seen as nothing more than a bundle of cells, the ethical issue of creating embryos for research purposes does not arise either: creating embryos for research is not a problem.

for research is destroyed before the 14th day following its creation.

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Opinion N°8, dated December 15, 1986 on Research and use of in-vitro human embryos for scientific and medical purposes.

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The exception concerns CCNE's comment on *therapeutic cloning*, see above, note 7.

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Opinion N°67, January 18, 2001 on the Preliminary draft revision of the laws on bioethics

Stating that the potential human being is an *enigma* means that, after hearing out these two extreme and mutually exclusive positions, however justified they might be in principle, one chooses to adopt an attitude which can truly cope with this difficult and essential *in between* concept: a “potential human being”.

Faced with this *enigma*, CCNE considered that there was no single and absolute response regarding the conduct to be adopted out of respect for the embryo; this conduct will depend on the context in which decisions have to be taken and what those decisions imply. “Ethical requirements cannot always be formulated in “absolute” dogmatic terms. Elaborating and implementing rules implies compromises made tolerable by the ethical principle of the lesser of two evils. The lesser evil, can be determined by weighing immediate and medium or long term risks and advantages, of a scientific, medical, psychological, social, cultural or philosophical nature¹¹.”

“The substantive position defended by the Committee is to recognise that the [human] embryo or [human] foetus has the status of a potential human being who must command universal respect. Successive Opinions on the subject seek to attune this demand for respect to other intents which are also ethically acceptable¹².”

In such a context, the issue of the possible destruction of embryos *in vitro* is not one which stands alone, in ethical isolation; it must first of all be considered in the context of the ethical issues which arise out of the particular circumstances which may lead to their destruction. For example, destroying embryos that are not going to be transferred following an ART procedure should not be viewed in the same light as destroying embryos in other and different circumstances.

In Opinion n° 8 of December 15, 1986 on *Research and use of in-vitro human embryos for scientific and medical purposes*, CCNE — before recommending the legal wording of a conditional authorisation — began by considering the issue of the destruction of spare embryos once the parental project had been dropped in ethical terms related to a *lesser evil*: “It is also possible to stress the contradiction embedded in in-vitro fertilisation which, acting to create life, is compelled at the same time to destroy life. [...] Destruction seems paradoxical in the case of a technique [ART] intended to create life. [...] The Committee considers that such destruction can only be envisaged as the *lesser of two evils* and that it is inevitable whenever conservation is not possible. Such destruction shocks those who consider that the life of embryos should be protected as soon as they are conceived.”

“Whenever the parents renounce their project or the project becomes impossible (for instance, due to separation of the couple), *the only solution considered by the Committee,*

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Opinion N°8, dated December 15, 1986 on Research and use of in-vitro human embryos for scientific and medical purposes.

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Opinion N°67, January 18, 2001 on the Preliminary draft revision of the laws on bioethics

as *the lesser of two evils*¹³, is destruction of the embryos (with the reservation of possible donations for research).”

It was in such a context that CCNE considered “compromises made tolerable by the ethical principle of the lesser of two evils¹⁴.”

D. Previous CCNE Opinions on human embryo destruction, research using embryonic cells and research on human embryos *in vitro*.

Ethical issues related to research on human embryos — and more generally to Assisted Reproductive Technology (ART) advances which led to fertilisation *in vitro* and the creation of embryos *in vitro* — have been central to **CCNE’s work from the start**.

In the **more than a quarter of a century** since CCNE’s creation, **over twenty of its Opinions** have been devoted to various ethical issues connected to human embryos or foetuses, such as Assisted Reproductive Technology (ART), which led to fertilisation *in vitro* and the conservation of spare embryos, or preimplantation genetic diagnosis, prenatal diagnosis, research on embryonic stem cells or on the embryo.

This was true of the first Opinion filed by CCNE, Opinion n° 1, dated May 22, 1984 on *Sampling of dead human embryonic and fetal tissue for therapeutic, diagnostic, and scientific purposes*.

Five other Opinions — starting with *Opinion N° 8*, dated December 15, 1986 up to *Opinion N° 67*, dated January 18, 2001 on the revision of the previous 1994 Bioethics law — dealt specifically with ethical issues connected to research on non transferred human embryos created *in vitro*, or research on cells from a human embryos after their destruction.

All of these various CCNE Opinions reflected, with a variety of developments, the major lines of *Opinion N° 1*, in particular:

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The *Etats Généraux de la Bioéthique* (as also the *Conseil d’Etat* and OPECST/*Office parlementaire d’évaluation des choix scientifiques et technologiques*) later formulated in legal terms the same recommendation as the one authored by CCNE in all of its earlier Opinions, i.e. *conditional authorisation*, in all of the following cases: for the destruction of embryos *in vitro* once a parental project has been abandoned, for research based on cells from destroyed embryos and for research on human embryos *in vitro* before their destruction.

But CCNE’s views, as expressed in previous Opinions, differed from those of the *Etats Généraux de la Bioéthique* in that they were significantly qualified on two essential points. On the one hand, CCNE has always considered the embryo *in vitro* as a “potential human person”, and not as an “incipient person”. On the other hand, CCNE has always considered that the destruction of embryos *in vitro* because a parental project has ceased to exist was the *only solution* that could be found as representing *the lesser evil*. This is a very different position from the one proposed by the *Etats Généraux de la Bioéthique*, which is an “all or nothing” stance, in which the ending of the parental project seems to remove any further ethical problem.

CCNE’s position, up to the present time, has been that this *solution* — which is open to question in that it depends on current ART modalities and constraints which, one may hope, will not remain static — is the *only solution* which can both embrace the complexities of ethical issues and respond to them as humanly as is possible, without obliterating them.

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Opinion N°8, dated December 15, 1986 on Research and use of in-vitro human embryos for scientific and medical purposes.

- rejecting the reification of human embryos and recognising the respect owed to embryos as “potential human persons”;
- rejecting the idea of “giving a normative definition” of human embryos;
- respect to be expressed by the nature of the conduct prescribed to deal with human embryos;
- a distinction between ethical issues and conducts authorised as a result of their preimplantation status, *in vitro*, or their development in their mothers’ body;

And made a number of **specific recommendations of a legal nature**, in particular:

- authorisation to destroy spare human embryos in the event of the parental project no longer being extant and in the absence of other couples wishing to host them;
- conditional authorisation for research on cells originating from human embryos destroyed *in vitro* according to stipulations described above;
- conditional authorisation for some kinds of research on human embryos conceived *in vitro*, before destruction is authorised according to stipulations described above;
- prohibition of the creation of human embryos for the purpose of research, together with “the introduction of an exception to this principle in the context of an evaluation of new Assisted Reproductive Technologies.”

E. Opinions expressed by various competent bodies over the last two years

The work done in preparation for the review of the law on bioethics dated August 6, 2004, has been the subject of a number of reports, including one by the *Conseil d’Orientation de l’Agence de la Biomédecine*¹⁵, CCNE’s own report¹⁶ and in particular reports containing recommendations of a legal nature, among them those by the *Office Parlementaire d’Evaluation des Choix Scientifiques et Technologiques (OPECST)* (*Parliamentary bureau for the evaluation of scientific and technological decisions*), the *Conseil d’Etat*, the Estates General on Bioethics and the *Mission d’Information Parlementaire* (*Parliamentary Advisory Mission*) on the revision of the bioethics law.

As regards specifically *research on embryos and embryonic stem cells*, the report by the Mission d’Information Parlementaire on the revision of the law on bioethics recommended that the current *prohibition of research with derogations* should be retained, whereas the OPECST, Conseil d’Etat and Estates General on Bioethics all recommended that prohibition should be replaced by *conditional authorisation* for research.

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Leçons d’expérience (2005-2008) et questionnements. (The lessons of experience (2005-2008) and questions.)

16

Opinion N°105, dated October 9, 2008. Questions for the Estates General on Bioethics

In this context, CCNE considered that the most useful contribution it could make at this time to society's and legislators' reflections on this subject, was to review the ethical issues in relation to research on human embryonic stem cells and research on human embryos, and to draw up in this way a general outline for reflection with the object of highlighting the ethical aspects of the various options, rather than make recommendations — as it had done previously and as many of the authorities recently consulted also did — on what the law should prescribe.

An absence of legal recommendations, however, **does not imply an absence of submission.** As we shall observe, in this Opinion, **specific recommendations will be formulated** with reference to the various issues; **in particular they will consist in drawing attention to the various essential ethical issues which need to be taken into account.**

CCNE insists on the importance of **finding a compromise, not as the result of being unable to choose, but on the contrary, as a reasoned response,** as behaviour that various opinions can choose to share, as a rejection of certitudes and instead, consideration of the full complexity of the enigma represented by “potential human person”, while granting full pride of place to parental projects involving human embryos in a human relationship that is the very condition for their future, even before their creation.

Along the same lines it has always chosen to pursue, in this instance CCNE's thinking bears on a fundamental issue which calls for conscientious discernment and response based on sober humility. Within CCNE, different positions are expressed originating in philosophical and religious foundations that are so difficult to reconcile that they appear to be mutually exclusive. **This document does not claim to rise above these dissenting positions; it seeks to pick out the path that society could follow to identify ethical issues and piece together the best possible solutions.**

This approach complies with one of CCNE's essential tasks, which is to help raise public awareness and encourage debate on ethical issues.

Consideration of the issues.

I. From *in vitro* fertilisation to research on human embryonic stem cells: an issue central to CCNE's deliberations since it was first created.

A. A revolution in assisted reproductive technology: *in vitro* fertilisation and the *in vitro* emergence of the embryo.

In the second half of the 20th century, advances in biomedical research and medicine made it possible, with the advent of contraception, not only to dissociate sexuality and procreation, but also, with *in vitro* fertilisation (IVF), to dissociate procreation from sexuality.

When IVF was developed in the framework of assisted reproductive technology (ART) to alleviate the distress caused to couples by infertility, a radically new situation arose: an embryo could be created, exist and begin to develop for a few days in a test tube (*in vitro*), *outside* the mother's womb and *before* implantation in the mother's body. This dissociation in both time and space led to the birth of Louise Brown, in 1978 in England, and to the birth of Amandine in 1982 in France.

This profound change, which came about due to the advances of ART in this country caused a great deal of perplexity and anxiety and led, early in 1983 to the creation of CCNE.

B. A radically novel discontinuity: dissociation of embryos and their mother, in both space and time.

Like many other biomedical advances, IVF, which suddenly made possible what had previously been thought of as impossible, raised new ethical issues.

What had until that time been a process of conception followed by a phase of continuous development within the mother's body, suddenly turned into a discontinuous process, beginning *before* and *elsewhere*, in a test tube. The maternal bond, in this first phase, was disincarnated at least to begin with, and was entirely replaced by its symbolic component — the parental project — under the temporary but complete control of biologists and doctors¹⁷ until the embryo was transferred.

This dissociation in time then took on an entirely and even more disturbing different dimension, with the development of freezing for embryos conceived *in vitro*, so that transfer to the mother's body could be deferred, leading in 1984 in Australia, to the birth of Zoe.

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In its Opinion n° 3, dated October 23, 1984, on Ethical problems arising out of artificial reproductive techniques, CCNE stated: "These new techniques open up uncharted territory. Procreation, that complex act, is dissociated. This act, which hitherto was decided and accomplished together by a man and a woman, conducted to its term by the association of the embryo and that woman, can now be a decision which is taken separately and at a different time. Others may play a role."

Not only could the embryo begin to live autonomously for several days outside the mother's body after *in vitro* fertilisation, but the freezing process (or cryopreservation) could suspend the course of development, and more radically the very course of life as a biological process. As a result, the very concept of a maximum *a priori* time limit between fertilisation and the beginning of pregnancy was eliminated.

For the first time, even before beginning to develop in their mother's body, it had become possible for human embryos to survive their genitors.

C. New ethical issues.

Up to this time, a characteristic feature of first the embryo and later the foetus, was its presence from the very start inside its mother's body. And it was the time of birth, i.e. the moment of separation from the mother, which legally defined the beginning of its existence as a person.

But IVF led to the emergence of an entirely new, transient and profoundly ambiguous situation where needed to be addressed the question of **situating human embryos which, for a certain time**, until they totalled a hundred or so cells, **were *not yet* in their mother's womb**, even though they were ***already* separated from it**.

Should embryos *in vitro* be viewed as identical to embryos *in vivo* in the same phase of development inside their mother's body? Should they be considered as being *not yet* entirely embryos, because this connection to the mother's body was missing? **Or, on the contrary, should they be seen as already *a little more than embryos***, because there was already a dimension of individuality due to the separation from the mother's body?

These different representations have never ceased to be jumbled together or be in conflict.

Other representations also became subject to question, extending beyond just embryos to include also the adults originating their creation. The **meaning of *parental project* took on a new dimension** since it had become necessary for it to pre-exist the embryo's conception outside the mother's body. And because the existence of this *parental project* was the actual condition for IVF to be practised as part of the ART process, its emotional and symbolic dimension became all the more important for being henceforth the only physical connection with the mother until the embryo was transferred to her body.

Similarly, the fact that an embryo was created and was, in the initial part of existence, isolated for the first time, signified that the biologists and doctors who had created it, on whom it depended entirely until the time came for implantation, were fully responsible actors committed to the embryo's future. And through their action, society itself, which had made it possible for them to be responsible for this very first phase of a human life, suddenly discovered itself to be in an entirely novel position of responsibility.

In this way, the new importance of the *parental project* was accompanied by the emergence of a new form of medical and social responsibility.

This unprecedented situation led to addressing new issues connected to the respective rights and duties of the couple who had formed the parental project and of society which had provided the conditions for the project to be implemented.

Should it be the mother, as is the case when the embryo develops within her own body, who alone has a right of decision over the embryo's future? Or the couple, because the future father and the future mother are still, at this point, connected in the same way to the embryo through the same symbolic parental project and the embryo is not yet within the mother's body? Or should it be society's decision, because at this point the future of the embryo, depends indirectly on society, through the action of its physicians?

These issues and their ethical repercussions have never ceased to be raised and discussed, at various levels and in various forms.

It was in this radically new context for the beginning of human life, which emerged over 30 years ago out of the advances of ART and against a background of efforts on the part of medicine and society to make it possible, despite infertility, for a parental project to see the light of day, that arose this new issue of the future of embryos *in vitro* when they were dissociated from their future mother in both space and time and not transferred.

D. The future of embryos created *in vitro* as part of an ART procedure, but which are not transferred.

There are at least two circumstances in which a medical decision is taken to refrain from transferring to the mother's body an embryo created *in vitro* via ART in the context of a parental project:

- when a major anomaly or arrested development is evidenced in an embryo *in vitro* before implantation;
- or when in the course of a pre-implantation genetic diagnosis (PGD), an embryo is found to be carrying the specific genetic sequence which motivated PGD research¹⁸.

In both of these circumstances, the human embryo is destroyed.

There is a third set of circumstances of a very different kind when the embryos created *in vitro* are not transferred: this is when the decision is taken to keep them by cryopreservation with the object of transferring them later in the event that the first transfer fails. **They then become what are called *spare embryos*, created by IVF as part of an ART procedure.**

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PGD is a very specific form of ART, in which the indication for IVF is not infertility, but is motivated by the parents' wish to abstain from transmitting to their child a genetic sequence leading to a particularly severe medical condition which is incurable at the time of diagnosis.

With IVF, the future mother (or the woman donating oocytes) must undergo hormonal hyperstimulation and ovarian puncture to retrieve the oocytes. This is an extremely taxing procedure and also endangers the mother's health.

Cryopreservation of spare embryos is designed to allow the parents to resort to ART procedures in the future in the event that the first pregnancy fails (the probability of childbirth occurring after IVF is still today less than around 20%), or if they wish to have another child at a later date, without having to go through the whole procedure involving hormonal hyperstimulation and egg retrieval again, and therefore avoiding additional risks to the health of the intended mother (or of the woman donating eggs)¹⁹.

But if the spare embryos, stored by cryopreservation, cease to be included in the parental project of the couple who were the originators of their creation, they are no longer just *spare* in the context of an ART procedure, following the initial implantation after IVF, they become *spare* — that is, “surplus” — to the parental project which was the origin of their creation. The same adjective — spare — designates two entirely different situations as regards the future of the human embryo. **Choosing two different adjectives would be semantically pertinent and would help to gain a better understanding of the ethical issues involved.**

It was in this situation, at a different and later time than the time of their creation, that arose the issue of *ceasing to preserve* the embryos, that is the issue of *their destruction*²⁰.

E. . From the creation of spare human embryos to the time they cease to be stored: an ethical issue in its own right, independently of the ethical issue of research using human embryonic cells.

The creation *in vitro*, as part of an ART procedure, of spare embryos and their storage by cryopreservation, was intended to solve a problem of medical ethics, i.e. preserving as much as possible the health of the future mother (or of the oocyte donor). But the inevitable *a priori* consequence raised another ethical issue, the future of spare embryos in the event of the couple forsaking their parental project (regardless of whether the cause was repeated ART failures, or on the contrary the birth of children, or the couple separating or the death of one or both partners, etc.).

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In *Opinion n° 107*, dated October 15, 2009 on *Ethical issues in connection with antenatal diagnosis: Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)*, CCNE remarked, in connection with PGD, that IVF “requires a fairly elaborate and invasive procedure (ovarian stimulation and puncture, etc.). “There are, on the one hand proven risks in hyperstimulation and ovarian puncture.”. And “It [IVF] is also a source of anxiety since at each stage of the procedure, there is a high risk of failure.”

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CCNE has used interchangeably the expressions “ending conservation” or “destruction” of spare embryos (see, for example, *Opinion n° 60*, dated June 25, 1998: *Re-examination of the laws on bioethics*

1. An ethical issue inherited from past practices...

One of the possible futures for spare embryos currently stored by cryopreservation, once the couple originating their creation have forsaken their parental project, is for another couple wanting ART treatment to *host* them. In this case, a woman unable to undergo IVF using her own eggs, asks for an another couple's spare embryo to be implanted, providing of course that the embryo's biological parents are in agreement²¹.

Another theoretical possibility to avoid destroying spare embryos once their genitors' parental project has been dropped would be to continue cryopreservation as long as possible, even indefinitely, leaving to others, at some future time, the responsibility of the embryos' future.

Apart from technical and economic feasibility, the ethical problem that would arise would be leaving to people who were not the couple originating their creation, or even leaving to future generations the burden of choosing what to do with the spare embryos.

The alternative would be to decide, after a specific period of time and subject to the couple's agreement, to end the conservation of spare embryos. In other words, to destroy them. The very question of how long that period of time should be already raises a complex issue²², as does the question of the relationship between the decisions taken by the couple themselves and those taken by the community.

As it happens, the solution that the cryopreservation of spare embryos as part of an ART procedure contributed to a problem of medical ethics — that is the wish to avoid endangering the health of the future mother — has created a different kind of ethical issue, that of the possibility of having to destroy spare embryos in the event of the

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This form of acceptance, which became possible in France with the law dated August 6, 2004, subject to approval by a court, occurs only very rarely for the time being. By way of comparison, since the procedure to adopt a spare embryo became legal, less than ten cases have been recorded, while out of the more than 150,000 spare embryos in cryopreservation at the end of 2007, there were 50,000 spare embryos for which there was no longer any parental project or whose genitors were not responding.

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The 2004 bioethics law provides for a maximum conservation of spare embryos for a period "at least equal to 5 years" if there is no response from the couple originating the embryo's creation to the annual letters sent asking them if they wish to pursue their parental project. In contrast, 25 years ago, CCNE in its Opinion N° 8, dated December 15, 1986, on *Research and use of in-vitro human embryos for scientific and medical purposes*, and the *Estates General on Bioethics*, in 2009 (Rapport des Etats Généraux de la Bioéthique. *Annexe 9. Les Contributions issues des forums régionaux. Avis citoyen du panel de Marseille. Etats Généraux de Bioéthique*) recommended a shorter maximum cryopreservation time for spare embryos, of no more than a year, renewable for one further period of a year.

parental project being abandoned²³. And this problem has grown proportionately with the extension of recourse to ART.

2. ... And an ethical issue as regards the practices of tomorrow.

To this reflection on a retrospective ethical problem, bearing on the way in which we can best act today to remedy a situation created in the past, must be added concern for the future.

As CCNE noted very recently, “the live birth success rate after oocyte retrieval is around 20% and there is little likelihood of this figure improving in years to come since it is in fact quite close to the figure for natural conception²⁴.”

Will subsequent ART progress allow bypassing the creation in future of spare embryos, as CCNE had expressed the hope already almost 25 years ago²⁵, — and therefore avoiding their conservation — without endangering the health of the future mother in the event of a failed pregnancy and new need of ART²⁶?

In the event of such progress, the question of the destruction of spare embryos would cease to be a problem connected to the use of ART, at least when the ART indication is a couple’s infertility.

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In its Opinion N° 8, dated December 15, 1986, on *Research and use of in-vitro human embryos for scientific and medical purposes*, CCNE remarked that “It is also possible to stress the contradiction embedded in in-vitro fertilisation which, acting to create life, is compelled at the same time to destroy life.” “Destruction seems paradoxical in the case of a technique [ART] intended to create life. From an ethical viewpoint, destruction, because it is deliberate, like fertilisation, can not be justified by the argument that, in nature, many embryos fail to nest. The Committee considers that such destruction can only be envisaged as the lesser of two evils and that it is inevitable whenever conservation is not possible. Such destruction shocks those who consider that the life of embryos should be protected as soon as they are conceived.” “Whenever the parents renounce their project or the project becomes impossible (for instance, due to separation of the couple), the only solution considered by the Committee, as the lesser of two evils, is destruction of the embryos (with the reservation of possible donations for research).”

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Opinion N°107 dated October 15, 2009, on *Ethical issues in connection with antenatal diagnosis: Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)*.

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In *Opinion N° 8*, dated December 15, 1986, on *Research and use of in-vitro human embryos for scientific and medical purposes*: “The Committee notes that the development of procreation by in-vitro fertilisation reinforces the trend which uses the human body as an instrument. Moreover, techniques such as the freezing of embryos increase the artificial nature of reproduction, especially as a result of the dissociation between conception and pregnancy. [...] One can envisage and hope that, in the future, research will allow fertilisation only of the necessary oocytes for transfer for the birth of a future child.”

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This question is connected in particular to the progress of research aiming to develop new assisted reproduction techniques, but such research is prohibited in France because it involves in principle, the creation of embryos for research purposes (see below, chapter IV. B. *The specific question of research for the evaluation of new ART procedures*).

But even if that came to pass, an entirely different indication for ART, that is PGD — which allows a couple to give birth to a child free of the genetic sequence or sequences which were identified as the cause of a severe and incurable genetic family defect, without the need for possible termination of the pregnancy — will have as a consequence the destruction of embryos conceived *in vitro* in a currently very small number of cases compared to the number of spare embryos stored using cryopreservation²⁷. (As a reminder, in a recent Opinion bearing on issues in connection with prenatal diagnosis, in particular PGD²⁸, CCNE recommended that PGD should continue to be practised as currently legally authorised and controlled).

And so, problems in connection with medical ethics have given rise to decisions to destroy embryos in the context of an ART procedure independently of any consideration of the possible use of embryos or of embryo cells for research purposes.

It was only much more recently, a little over 10 years ago, that embryonic human stem cells suddenly became of major scientific interest for a whole chapter of biomedical research, which led to considering human embryos as a potentially important source of stem cells for research.

F. From the ethical issue of the destruction of non transferred embryos to the ethical issue of research using embryonic stem cells.

In 1998, 20 years after the birth of Louise Brown, the entirely new question arose of the possibility and scientific worth of doing research on stem cells from destroyed human embryos. Research at the time indicated that human embryonic stem cells — as was also the case for mouse embryo stem cells, a discovery made in the 1980s — could be isolated and cultured *in vitro*, be renewed *in vitro*, and give birth *in vitro*, depending on the environment provided for them, to almost all, if not to all, the more than two hundred different cells types contained in an adult human body.

1. Beginnings, means and ends.

One of the theoretically possible ways of obtaining embryonic stem cell lines from embryos *in vitro*, without destroying the embryos, could be using the cell (or the two cells) which are sampled when PGD is performed on an embryo *in vitro* which turns out to be free of the genetic defect under investigation and which will therefore be transferred.

Despite research in this field, it has not been possible so far for technical reasons to derive embryonic stem cell lines using the cell or the two cells sampled from a human embryo when PGD is performed. **If it becomes possible in the future to overcome these technical**

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Between 150 and 200 IVFs per year (leading to some 50 births per year) were performed as part of a PGD in France in 2006 and 2007.

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Opinion N°107 dated October 15, 2009, on *Ethical issues in connection with antenatal diagnosis: Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)*.

obstacles, research on embryonic stem cells would no longer need to be done using cells from embryos that had been destroyed²⁹.

But for the time being, research on human embryonic stem cells is only possible using a destroyed human embryo.

And there are at least two circumstances, very different as regards their ethical implications, in which such research could be undertaken:

- Using for research purposes, cells isolated when a spare embryo created *in vitro* via ART is destroyed and not transferred, and when destruction is decided for reasons unconnected with the possibility of doing research.
- The creation *in vitro* of a human embryo for the sole purpose of destroying it in order to use its cells for research.

This second approach is radically different from the first case, in particular from the point of view of the reification of a human embryo: in this instance, the intention of research is the cause of both its creation and its destruction.

2. A particular case of creation of a human embryo *in vitro*: nuclear transfer in the context of so-called *therapeutic cloning*.

A discovery in 1996 led to considering the possibility of performing a radically new kind of research on embryonic cells: '*reproductive cloning*' gave birth to the first ever cloned mammal, Dolly the sheep. The *cloning* process consisted in creating *in vitro* an embryo, genetically identical to an adult ewe, by transferring the nucleus of a cell of the adult ewe to an oocyte from which the nucleus had been removed.

In theory, this approach provided for the first time a new possibility, that of being able to create *in vitro* human embryos genetically identical to the cells of a particular adult person and to extract embryonic stem cells from the embryos which are destroyed. The discovery — although at the time no one knew whether it could apply to human cells — on the one hand raised international censure regarding the possibility of its use in the context of ART with the aim of giving birth to children by '*reproductive cloning*'; and on the other hand, led to projects for purely scientific purposes involving the creation of embryos *in vitro* by nuclear transfer of human cells to human oocytes, thus raising the issue of creating embryos *in vitro*

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A great deal of importance has been attached sometimes to the ethical value of such technical progress. However, it would not solve at all the issue of the destruction of embryos in the context of PGD. In fact, a situation would ensue where the link between embryo destruction and research on embryonic cells would be maintained, albeit indirectly. PGD, which leads to destruction for medical reasons of certain embryos created *in vitro*, would also become a way to make available for research embryonic cells sampled from live embryos, free of the genetic defect under investigation and therefore about to be implanted. But it is not because research on embryonic cells could be performed using live embryos that the ethical issue could be solved of the destruction for medical reasons in the context of PGD of embryos created *in vitro* and carriers of the genetic defect investigated by PGD.

However, from a medical point of view, if such progress could one day be made, it would then become possible to derive and use such cells for the possible benefit of the embryo from which the cell lines were derived during PGD.

for the sole purpose of destroying them in order to try and isolate embryonic stem cells for research.

One of the objectives was to be able, if required, to use these cells at some later date to administer medical treatment to the person whose cells had provided the nucleus used in the transfer, since the genetic identity between the embryonic stem cells and the patient made it likely that these cells would not give rise to immune rejection. As a result, an inappropriate and premature name was chosen for the technique: *'therapeutic cloning'*, which purposely introduced a confusion between a technique — nuclear transfer — and a research approach — *cloning for scientific purposes* — with one of the possible applications that could be hoped for at some future time, that is treating severe and as yet incurable diseases.

The major ethical issue presented by *cloning for scientific purposes* is the creation of embryos *in vitro* with the sole aim of destroying them so as to be able to use their cells for research.

For some currents of opinion, the major ethical issue is not so much the creation of embryos *in vitro* for the sole purpose of research, but rather the possible use of such research by people wishing to apply the nuclear transfer technique in the context of ART in order to arrive at so-called *'reproductive cloning'*.

In other sectors of opinion, there is no major ethical issue since the embryo was not created by fertilisation and is therefore *less than* or *different from* an embryo³⁰.

Be that as it may, one of the ethical issues raised by these activities, and everyone can agree with this, is the fact that human oocytes must be obtained, so that women are exposed to the risk of ovarian stimulation and oocyte retrieval without any medically assisted reproduction project being involved, either for the benefit of the couple concerned or for another couple.

3. *Cybrids*: a scientific solution (and a new ethical problem) for an ethical issue created by a scientific advance?

A comment in CCNE's *Opinion N° 8* dated December 15, 1986 on *Research and use of in-vitro human embryos for scientific and medical purposes*, noted that certain people believed: "that if science generates problems, more science will solve them³¹." Almost a century ago, the geneticist John Haldane likened this vision of science to the myth of *Daedalus*³², as

³⁰ In its *Opinion n° 67*, dated January 18, 2001 on *The preliminary draft revision of the laws on bioethics*, CCNE remarked on the issue of ethical problems arising out of "therapeutic cloning" and mentioned that its members had not reached agreement on this point. CCNE's conclusion was the following: "On the subject of therapeutic cloning, however, opinions differ. There is general agreement that this subject raises extremely difficult ethical issues, but members of CCNE are divided, depending on their vision of the world and of the future, between two positions which have been outlined above. There is a majority in favour of the second of these positions, i.e. the one which favours controlled authorisation to engage in 'therapeutic' cloning."

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Comment by France Quééré.

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Daedalus never ceased to try and solve with new scientific and technical inventions the problems caused by each of his previous inventions³³.

An example of this is a scientific approach which was put forward to solve the ethical issue raised by so-called ‘*therapeutic cloning*’: that is the need to use human eggs to obtain the human embryonic stem cells genetically identical to a certain person, using the nuclear transfer technique. The suggested solution was the production of *cybrids*, i.e. a hybrid human-animal embryo, by transferring the nucleus of a human cell to the cytoplasm (hence the *cy* prefix) of an animal oocyte from which the nucleus had been previously removed.

But the possible creation of these *cybrids* raised new scientific issues and new ethical issues³⁴. **The rapid succession and accumulation of these various scientific and technical developments** — creation of human embryos *in vitro* by fertilisation for research purposes; creation of human embryos *in vitro* by nuclear transfer for research purposes; creation *in vitro* of *cybrids* for research purposes — **and the dizzying emphasis in announcements of expectations of major therapeutic applications gave rise to concern on what limits should apply and to fears that the world of ethics had lost its bearings.**

In this paper read in 1923, entitled (and published under that same title) *Daedalus, or, Science and the Future*, Haldane compares the myth of Daedalus the inventor, a prototype of modern scientists, to the myth of Prometheus, the transgressor, who stole fire from the gods (quoted by Henri Atlan, in *L’utérus artificiel*, Seuil, 2005.).

François Jacob also referred to the myth of Daedalus in his *La souris, la mouche et l’homme* (1997, Odile Jacob), as a metaphor for “an ailment of our time” and in particular stated that: “With Daedalus, science without a conscience is emerging.”

³³As a reminder, Daedalus built a device so that the queen of Crete, Pasiphaë, the wife of King Minos, could mate with the sacred bull that the god Poseidon had made her fall madly in love with, to take revenge on Minos. The Minotaur, half man and half bull, a chimera devouring men for sustenance, was born of this union. Minos then asked Daedalus to construct a prison for the monster, the Labyrinth. Then it was Daedalus again who gave Minos’ daughter Ariadne, who was in love with Theseus, the thread (Ariadne’s thread) enabling Theseus to escape from the Labyrinth after killing the Minotaur. Minos punished Daedalus and his son Icarus by imprisoning them in the Labyrinth. Daedalus, the inventor of glue, then crafted wings out of birds’ feathers stuck together. With the help of their wings, they flew out of the Labyrinth and escaped, but Icarus ignored the cautionary advice he had been given and flew too close to the sun so that the wax holding his wings together melted and he fell to his death in the sea. And so the succession of Daedalus’ inventions, each one of which was a remedy for the problems caused by his previous inventions, closed (for the while) on this tragedy.

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From a scientific point of view, there was the question of possible effects on these cells (and therefore of possible effects on their possible future use for *therapeutic* purposes) of the coexistence in the same cell of an animal cytoplasm, in particular mitochondria (and their genes) which are present in the cytoplasm, with a human nucleus and genome.

Ethically, this possibility was the cause of serious misgivings at the idea of a creation very close to a *chimera*. Would this be a degradation of the beginning of human life? Or would it be the beginning of non human life?

The prospect of such an approach raised, in even more disquieting terms than the prospect of human ‘*reproductive cloning*’, the fear of the possibility of a transfer (either to an animal, or *a fortiori*, to a woman) to await the birth of *cybrids* created *in vitro*, and therefore the issue of how to prohibit such actions effectively and absolutely.

It was in this context of radically new and rapidly evolving scientific developments, of spectacular announcements of possible medical and therapeutic applications and growing concern about ethics that the consultations and debates took place regarding the revision of the 1994 law on bioethics, followed by the framing of the 2004 law.

G. From embryonic stem cells to adult stem cells: recent developments in research using non embryonic human stem cells.

Leaving aside spectacular and premature announcements for effect, **research on human stem cells had begun, in the last ten years or so, to branch out into a real scientific revolution.**

1. An ancestral property of life itself.

In simplified terms, stem cells are highly fertile and have great plasticity, meaning that they are highly capable of renewal and of giving birth to different cells.

In very general terms, it was in the form of stem cells that life has propagated since its dawn, over 3.5 billion years ago. Unicellular organisms, which were the only life forms in the first phases of evolutionary life, were composed of stem cells, capable of both renewal and a certain degree of plasticity. The subsequent emergence of multicellular animals and plants went together, for animals in particular, with a progressive reduction of the cells' capacity for renewal as they constructed the complexity of a body and with a considerable increase of their capacity to give rise to diversity. It is at the beginning of our embryonic development that our stem cells possess their greatest fertility potential and their greatest diversification potential, giving rise gradually to the over two hundred families of different cells composing our bodies.

2. The *epigenetic* revolution, or the effects of the environment on the way our genes are used.

The name of the major research domain currently exploring these matters is *epigenetics*. This is the study of the interaction between genes and their environment and is a rapidly expanding field of scientific activity.

Literally, *epigenetic* means what is *above* genes, *beyond* genes, i.e. the effect of various environmental factors on the way in which cells and bodies use their genes.

One of the essential, ancestral and universal dimensions of life's complexity is the capacity that genetically identical cells have of using their genes in very different ways depending on their environment and their background, leading to a diversification of the characteristics and potentialities of cells, which we call cellular differentiation.

One of our liver cells is very different from one of our skin cells, or one in our heart or our brain. The differences between these genetically identical cells are due to the fact that they do not use the same genes. Born of the same initial cell (the result of fusion between a spermatozoon and an oocyte), later of the same embryonic stem cells, their history and their environment have had as a consequence that most of their twenty thousand genes have

become inaccessible; but the same genes did not become inaccessible in liver, skin or brain cells. This inaccessibility is due to enzymatic reactions which brought about chemical modifications in various regions of the DNA and the proteins around the DNA, modifications which are potentially reversible but very stable and which are passed along by inheritance throughout the successive cellular generations. A liver cell almost always give birth in the body to another liver cell, skin cell to skin cell... and not to an embryo. Thus, the complexity of our bodies is born of a vast process of differential subtraction of the possibilities of using our genes, producing a mosaic of over two hundred different modes of subtraction and giving birth to the diversity of over two hundred families of body cells.

In the earliest few days of embryonic development, each cell of the embryo is able, if it is isolated from the embryo, of giving birth unassisted to a new embryo; these cells are described as being *totipotent*.

Starting with the 5th day of development, the cells located on the periphery of the embryo have become *trophoblasts*, the cells which anchor to the uterine mucous membrane and so allow the implantation of the embryo. They will contribute to the formation of the placenta, this essential bridge or bond between the embryo and its mother.

The cells in the centre of the sphere forming the embryo are called *embryonic stem cells* and they will give rise to all the cells in the body, but they are no longer capable of developing into *trophoblasts*; none of these embryonic stem cells can spontaneously produce a new embryo. These cells are described as *pluripotent*.

As development continues, the potential to differentiate of the stem cells will be further restricted; they become *multipotent* and for some of them, *unipotent* which means that they are capable of giving rise to only one family of body cells. Some of the body's stem cells, after we are born, are *multipotent*, others are *unipotent*, but to the best of today's scientific knowledge, they have all lost their *pluripotency* (at least spontaneously, see chapter 4 below) and *a fortiori* their *totipotency*.

3. From the cell to the embryo, or from a scientific fact to an ethical issue.

The first appearance of a human embryo is in the form of a single cell, born of the fusion of two cells (an oocyte and a spermatozoon).

This first cell, all on its own, is a human embryo.

Later this cell will give birth to new cells and each of these first generations of *totipotent* cells, making up the embryo, will keep this capacity of giving birth on their own to a new embryo if they are isolated from neighbouring cells (as mentioned above). At this point they are components of the embryo, as long as they remain in the embryo, but they are also the possible origin of a new embryo if they are separated from the original embryo. If they are isolated *in vitro* from the embryo they are components of, they will proceed, depending on the environment they are given *in vitro*, either to spontaneously irreversible transformation into pluripotent stem cells, or to the construction of a new embryo.

These totipotent cells, once they are isolated from the embryo, could be viewed as the *potentiality* of a human embryo, in other words — if one chooses the wording that CCNE used to characterise the human embryo — as the *potentiality* of a “*potential human person*.”

As the cells proceed to give rise to new cells, they will lose this potentiality and a frontier will appear between the embryo as such and each of the cells which compose it.

At this point, the embryo can no longer be reborn of its constituents.

Therefore science seems to make it possible in this case to operate a clear distinction, in ethical terms, based on the spontaneous potentialities of the cells depending on the phase of development of the embryo *in vitro* (but for a debate of this issue in a broader, and more complex context, see below, *Prospective reflection: ethical issues raised by research on non embryonic human stem cells*).

4. From an imitation of nature to the discovery of novelty.

There are at least two major scientific questions arising with reference to stem cells:

- The first relates to the nature of the molecular mechanisms underlying their capacity to give birth to other identical stem cells, that is their capacity for renewal.
- A second question relates to the nature of the molecular mechanisms underlying their plasticity, their repertoire, that is the diversity of the cell families to which they can give birth.

A spectacular illustration of the effects of the environment on the way in which genes can be used was given by the experiments on nuclear transfer (or cloning) mentioned above: the nucleus of a skin cell transplanted to an oocyte cytoplasm from which the nucleus has been removed will enable genes to be used leading to the creation of an embryo.

Where are the boundaries of cellular plasticity? What are the specific features of molecular composition or structure of the cellular body (the cytoplasm) of an oocyte which allow it, once it is fertilised, to give birth to embryonic stem cells, while a skin cell which has the same genes is incapable of doing so spontaneously?

Up to what point can modifications to the environment, in some or most of the adult body's cells, restore the initial potentialities that the environment of the developing body seemed to have progressively frozen?

Research on human stem cells has progressed in four major directions:

- **The first two of these consisted in imitating nature.**

To begin with, for over 30 years, by using the spontaneous properties of multipotency of certain stem cells in the adult body, i.e. the hematopoietic stem cells in bone marrow, to reconstitute with remarkable therapeutic efficacy, the production of all blood cells by bone marrow transplantation.

And much more recently, by attempting with remarkable success in the field of research, to incite pluripotent embryonic stem cells extracted from their natural environment, to take the path *in vitro* which they normally take spontaneously inside a body in construction, leading to their transformation into the over two hundred different families of cells which compose an adult body.

- **A third** research approach sought to explore to what degree spontaneously multipotent cells, which are found in umbilical cord blood (or cells from the umbilical cord itself) of newborns, could be capable of transformation into some of the cell families present in the adult body once they were extracted from their natural environment. Recent work has shown that the stem cells in bone marrow or cord blood could spontaneously evolve into skin, digestive tract or blood vessel cells in the bodies of patients in which they were transplanted to effect a cure (see above). Other recent results would suggest that factors added *in vitro* to cord blood cells could transform them into a number of different cell populations, such as pancreatic or nerve cells.

- Finally, **yet other and quite different research**, consisted in attempting to modify artificially the epigenetic characteristics of certain cells in the adult body and induce them to follow differentiating paths (or rather dedifferentiating paths) other than those they usually follow in our body.

In this way, since 2006 from mouse cells and since 2007 for human cells, spectacular and unexpected progress has been made: the transformation of differentiated cells of an adult body into *pluripotent* stem cells (*iPS*, or *induced pluripotent stem cells*), endowed with properties similar to those of embryonic *pluripotent* stem cells.

With this kind of manipulation it becomes possible to induce a cell from an adult human body along a course of dedifferentiation *in vitro*, although this was previously thought to be impossible in animals, and transform them into cells possessing all (or almost all?) the characteristics of human *pluripotent* stem cells, without having to pass through the embryo formation phase.

In fact, all that is needed is to force skin cells (fibroblasts for example) to use four of their genes which had spontaneously become inaccessible to them. These four genes are used by embryonic stem cells in the first phases of embryo development. This resumption of the capacity of skin cells to use the four genes (for the time being, by artificially introducing extra copies of the genes into the cells) makes it possible for a small fraction of these adult skin cells to acquire similar stem cell properties to those of *pluripotent* embryonic stem cells. In other words they are capable of self-renewal and, in an appropriate *in vitro* environment, of giving birth to most, or even all of the 200 cell families constituting adult human bodies.

Research involving adult somatic stem cells has implications which overturn many concepts which so far were considered to be well established³⁵.

As regards *ageing* for instance, recent work indicates that *iPS* stem cells, with their capacity for *pluripotency* and renewal which seem similar to those of embryonic stem cells, can be obtained from the skin cells of people over the age of 80. The so-called “aged” nature of these cells is not therefore due to intrinsic wearing out of the cells. Rather, it is because they belong to the environment of a person over 80 years of age that they are “senescent”. If they are given the opportunity of using four of their genes that their history and their environment had made unavailable to them, they recover “youthful” properties similar to those of embryonic stem cells. In other words, at least a part of the potentialities which characterise the “youth” and “age” of these cells appears to be not so much an intrinsic characteristic as an “update” of potentialities, reversible by the environment.

For *cancers*, recent work indicates that, on the one hand, cancers emerge not only out of genetic alteration to normal stem cells, but also out of epigenetic alteration, modifying not so much the cellular gene sequence as the cell’s capacity to use some of its genes. And, on the other hand, that many cancers are made up

These major scientific ventures — imitating spontaneous cellular differentiation processes in the course of development, or inventing new forms of cellular differentiation — **are now proceeding in parallel and complementarily, with their respective advances acting in mutual enrichment as they progress in the exploration of an unknown continent, whose borders no one is capable of defining at this time.**

H. Research on embryonic cells and research on human embryos: an issue central to CCNE's deliberations since it was first created.

Since its creation in 1983, CCNE has devoted a significant amount of its time to ethical issues involving the embryo or the foetus. **These deliberations have given rise, in over a quarter of a century, to more than twenty Opinions**, broaching various ethical issues involving human embryos and foetuses, ranging from ART procedures, preimplantation diagnosis, prenatal diagnosis, to research on embryonic stem cells or on embryos.

Six of the Opinions concerned specifically research on human embryo cells and on *in vitro* human embryos.

Such was the case in the **very first Opinion CCNE published**, *Opinion n° 1*, dated May 22, 1984 on *Sampling of dead human embryonic and foetal tissue for therapeutic, diagnostic, and scientific purposes*.

In this *Opinion N° 1*, some of CCNE's statements seem at first sight to be in contradiction:

- On the one hand, CCNE stated that “The embryo or foetus must be recognised as a *potential human person* who is or was alive and who must be respected by all concerned.”
- On the other hand, CCNE recommended authorisation of research on dead embryos, providing in particular that parents did not object.
- Finally, CCNE recommended a distinction to be made between embryos *in vitro* and embryos *in vivo* after implantation in the mother's body, specifying that “As far as ethical problems arising out of the use of human embryos are concerned, they are of a different nature in each of the two phases which must therefore be dealt with differently³⁶”, and that considerations regarding

of a tiny subpopulation of cancerous stem cells, giving birth not only to the very large population of cancerous cells which invade the body, age and disappear, but also to the tiny population of new stem cells responsible for the renewal and propagation of the cancer. These discoveries suggest that the efficacy or failure of cancer therapy could depend on its ability to target this small subpopulation of stem cells.

There is another reference to this distinction in both French and European law, in an entirely different form, concerning the legal protection of embryos. In France, Article 16 of the *Code Civil* states that the law “guarantees the respect of the human being from the very start of life.” But the *Conseil Constitutionnel* (Constitutional Council of the French Republic) (decision of July 27, 1994) states that “legislators provided many safeguards for the conception, implantation and conservation of fertilised embryos *in vitro*” but “did not consider that “all embryos already formed should be stored, regardless of circumstances and for an indefinite time; [...] they considered that the principle of respect for all human beings from the beginning of life did not apply to them.” As for the European Court of Human Rights, they decided (July 8, 2004, Judgment *Vo v. France*, paragraph 82) that “the issue of when the right to life begins comes within the margin of appreciation which the Court generally considers that States should enjoy in this sphere”.

specifically embryos *in vitro* would be the subject of a further Opinion.

Five Opinions — the first of which was *Opinion N° 8*, dated December 15, 1986, and the last, *Opinion N° 67* of January 18, 2001, on the subject of the revision of the previous 1994 law on Bioethics — **deal specifically with ethical issues in connection with research on human embryos created *in vitro* and not transferred, or with research on cells originating from these human embryos after their destruction.**

These opinions refer to, and develop in various forms, the reflections and recommendations contained in *Opinion N° 1*.

For example, *Opinion N° 8* dated December 15 1986, on *Research and use of in-vitro human embryos for scientific and medical purposes*:

- States that “From the time it has been conceived the human embryo is a being and not a possession, a person, not a thing nor an animal. It should be considered as a would be subject, as an "other" of which we cannot dispose and whose dignity defines limitations for the power or control of others” and that “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. [...]Such consideration should take precedence over the advantages that might result from using human beings as though they were objects, even though it represents potential for the improvement of medical knowledge and furtherment of science. Respect for human dignity must guide both the development of knowledge and the limits or rules to be observed by research.”
- But it specifies that “Ethical requirements cannot always be formulated in "absolute" dogmatic terms³⁷.”
- It rejects the creation of human embryos for the purpose of research³⁸.
- But “However, it is of the opinion that the donation of spare embryos for research is acceptable provided it is strictly regulated³⁹.”

³⁷“Elaborating and implementing rules implies compromises made tolerable by the ethical principle of the lesser of two evils. The lesser evil, can be determined by weighing immediate and medium or long term risks and advantages, of a scientific, medical, psychological, social, cultural or philosophical nature.”

However, the Opinion does introduce the idea of possible derogation from this prohibition in the context of ART: “Fertilisation of oocytes for research is not possible. It would be contrary to the principle described above. It is, however, possible to envisage that oocytes could be fertilised with the husband's sperm (excluding cross fertilisation test) with a view to establishing a diagnosis. It is up to the couple to decide, with the doctor's approval, whether such embryos should be implanted, destroyed or donated for research purposes, exactly as if they were excess embryos. Such embryos are dealt with according to the rules described above.” This possibility of derogation was taken up again and expanded upon fifteen years later in *Opinion N° 67*.

Opinion N° 53, dated March 11, 1997 on *The establishment of collections of human embryo cells and their use for therapeutic or scientific purposes* (which preceded by one year the discovery of pluripotent human stem cells derived from the destruction of embryos created *in vitro*) lists its recommendations in a prospective reflection⁴⁰: “...only frozen embryos donated by couples who have given written consent, forsaken their parental project and decided to put an end to conservation, could be used for research.” And “...any creation de novo of human embryos for any purpose other than a parental project, is still not permitted.”

Finally, *Opinion N° 67*, dated January 18, 2001 on the *Preliminary draft revision of the laws on bioethics*:

- Begins by recalling that “The issues of legitimacy and of ethical limits to research on the human embryo were addressed in the early days of CCNE, and the Committee has given much thought and published several reasoned Opinions on this subject. Its consideration is part of a philosophical and ethical debate which has not ripened to a conclusion and may never do so. The substantive position defended by the Committee is to recognise that the embryo or foetus has the status of a potential human being who must command universal respect. Successive Opinions on the subject seek to attune this demand for respect to other intents which are also ethically acceptable.”
- It then addresses the issue of research on embryonic stem cells⁴¹. It refers to the distinction made in *Opinion N° 1* between the pre-implantation *in vitro* phase and the *in vivo* phase, after transfer⁴² and the

“The Committee states inter alia that the purpose of human fertilisation is first and foremost procreative and cannot ignore the benefit for a child to be born, nor its right to be born to a united couple. The use of so-called spare embryos for research purposes can only be secondary when it has become patently impossible to transfer all the embryos”.

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“Human stem cells of this kind, equivalent to ES cells in mice, do not exist as yet, but several laboratories outside France are working on their creation. Thus, the CCNE considers that its mission demands that it should as of now formulate recommendations on the conditions according to which they could, possibly, be established and used.”

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“This point represents the main ethical debate. As mentioned above, as early as 1997 the Committee pronounced itself in favour of the removal of legal obstacles which, up to the present day, prevented French researchers from constituting embryonic stem cell lines unless the embryos or foetuses were the result of spontaneous or induced abortions. [...] (Opinion n° 53 on the creation of human embryonic organ and tissue collections and their use for scientific purposes). Rapidly developing scientific progress, opening up therapeutic possibilities, motivated this position. Since then, such hopes were amply met, at an even faster rate than was expected at the time. For this reason the Committee approves the fact that the preliminary draft authorises researchers to use spare embryos as a source of stem cells. CCNE believes that two essential considerations must regulate this possibility. The first is that only embryos with no reproductive future can be viewed as available for this purpose. The second is that being subject to the constitution of stem cell lines cannot, for any reason and in whatever form, serve to give these embryos a new reproductive future.”

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“CCNE has always refused to attach normative definition to the embryo based on specifically defined biological stages. Similarly, legislation had so far refrained from distinguishing between phases in the development which follows the first division of the fertilised egg. In order to set a limit to *in vitro* development of embryos intended for the constitution of stem cell lines, the preliminary draft innovates in that it introduces a reference to a stage of development, that of tissue differentiation. CCNE understands the reasoning, but suggests the adoption of clearer references in biological terms.

rejection of reifying the embryo *in vitro*⁴³.

• And it concludes the “Main points of agreement include:

◦ firm reminder of the principle that creation of human embryos for the purpose of research is prohibited⁴⁴;

◦ controlled possibilities for the use of spare IVF embryos for research purposes, in particular research on embryonic stem cells.”

And so we find that these various CCNE Opinions have all adopted the main lines of the position expressed as far back as in *Opinion N° 1*, recommending all of the following:

- **Rejection of the reification of human embryos and a recognition of the respect owed to them as “potential human persons”;**
- **Refusal to “attach normative definition” to human embryos;**
- **Respect expressed by the nature of the way in which it is recommended they be treated;**
- **Distinction made between the embryos’ status in the pre-implantation phase, *in vitro*, and the phase of embryo development within the mother’s body, as regards ethical issues and the way in which embryos may be treated;**
- **Rejection of creating human embryos for the purpose of research⁴⁵;**

In its view, tissue differentiation is in fact an abstract and ambiguous reference, since it relates to a continuing process, rather than to a specific stage of development. For instance, depending on whether one considers the moment when tissues that will become the placenta differentiate from those which will become the inner cell mass, or the moment when one or the other embryonic tissue differentiates, these events occur at very different times in the process of development. Conversely, implantation of the embryo into the uterus is a major single event. The Committee therefore recommends that instead of the proposed reference, a reference designating the end of the pre-implantation stage should be preferred, i.e. the moment when the embryo acquires the capacity to implant in the uterus.”

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“Introducing a reference of this nature should not however in CCNE's view, give any support to those who consider that the embryo can be reified in the early phases of its development. It would be just as excessive to consider the pre-implantation embryo as simply a bundle of cells of human origin, as to consider it sacred because it is a potential human person. The notion of "ongoing embryonic process" could perhaps represent the enigma which veils the exact nature of the embryo in the very first moments of life. Be that as it may, and precisely because of this enigma, the Committee declares its attachment to the view that the human embryo must, as soon as it is formed, receive the respect owed to its status.”

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But there is also agreement (as in Opinion N° 8) on “the introduction of an exception to this principle in the context of evaluation of new medically assisted reproduction techniques.”

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With the possibility of an exception, cf previous footnote.

- **Authorisation to destroy human embryos in excess when parental projects are forsaken and no other couple wishes to host them;**
- **and conditional authorisation, in this context, for some research to be performed on human embryos conceived *in vitro* before their destruction and on cells from human embryos conceived *in vitro* and destroyed before transfer.**

The destruction of embryos which were created in the context of medically assisted reproduction techniques, but are not implanted, is the issue on which we shall focus with the 2004 Law on bioethics as our starting point.

II. Research on human embryonic *cells* after destruction of the embryo previously created *in vitro* as part of an ART procedure: ethical reflection in the context of the 2004 law on bioethics.

A. The destruction of embryos which have not been transferred is authorised by law⁴⁶...

In the event that in the course of PGD, an embryo is found to be a carrier for the genetic sequence which had motivated the procedure, the law stipulates that the embryo will not be transferred, with the result that this absence of transfer in fact leads to embryo destruction.

In the more complex situation where surplus embryos which are no longer included in the parental project of the couple who had initiated their creation as part of an ART procedure, the 2004 Bioethics Law provides for two possibilities:

- If the couple who had initiated the creation of the embryo agrees to allow the frozen surplus embryo to be donated to a host couple who have explicitly made a request to that effect, and their request has been approved by a judge, the embryo may be transferred.
- If that is not the case, the couple who had originated the embryo's creation may, at any time, request that the embryo cease to be preserved, leading therefore to the destruction of the cryopreserved surplus embryo. If the couple (or one of its partners) originating the creation of the embryo does not respond to the letters sent to them each year asking whether their parental project still stands, or in the event that the members of the couple disagree about continuing their parental project or disagree on what is to be done with the surplus cryopreserved embryo, it will be destroyed after "at least five years" of conservation, unless the biological parents oppose its destruction.

In other words, if the couple originating the creation of embryos *in vitro* as part of an ART procedure do not wish to pursue their parental project, the law authorises putting

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an end to conservation, and therefore the destruction of the surplus embryos, at any time at the couple's request, or within five years following cryopreservation of surplus embryos, providing the couple concerned abstain from expressing their opposition to destruction⁴⁷.

B. ... but the same law prohibits research on cells from human embryos that have been destroyed.

And yet, as regards the possibility of research on cells from the destroyed human embryo, not only is the absence of opposition on the part of the couple concerned insufficient to allow it, but the couple's express agreement is also insufficient, since any research on destroyed human embryos or the cells from such embryos is prohibited by law.

There is, however, an exception to this prohibition since the law provides for the possibility of authorisation to be given by the *Agence de la Biomédecine*, **on a case by case basis**, for research on the cells of a destroyed embryo, subject in particular to the couple concerned consenting to such research and if "the research could lead to major therapeutic advances" and "there is no alternative method of comparable efficacy".

This is also true in the two other situations in which embryos are to be destroyed immediately after their creation *in vitro*, and where there will be no possibility of deferred transfer — i.e. the evidence *in vitro* of a major defect or of interrupted development of the embryo, or the detection in an embryo of the genetic anomaly that was the subject of PGD.

The intention of lawmakers when they prohibited research, was to eliminate any possibility of instrumentalisation of spare embryos. **The subject for additional reflection on this point is considering the questions that come to mind on reading the text of the law, as regards the meaning of prohibition applying specifically to research.**

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Article L2141-4, modified by Law ([Loi n°2004-800 du 6 août 2004 - art. 24 JORF 7 août 2004](#))

The two members of the couple whose embryos are preserved are asked in writing every year whether they wish to pursue their parental project.

If they no longer have a parental project or if one of them has died, the two members of the couple or the surviving member, may consent to their embryos being donated to another couple in accordance with the conditions set out in articles L. 2141-5 and L. 2141-6, or for those embryos to be the subject of research in accordance with the conditions set out in article L. 2151-5, or for cryopreservation of those embryos to cease. In each of these events, consent and/or requests must be expressed in writing and be confirmed in writing after three months delay allowed for reflection.

In the event that one of the members of the couple has been consulted on several occasions and has not responded to the question of whether he or she wishes to pursue the parental project, the embryos cease to be preserved if the time of conservation is at least equal to five years. This is also the case if the members of the couple disagree regarding continuance of the parental project or on what is to be done with the embryos.

When both members of the couple, or the surviving member of the couple, have consented, in accordance with conditions set out in articles L. 2141-5 and L. 2141-6, for their embryos to be hosted by another couple and no donation has been made after five years have elapsed since the day on which consent was expressed in writing, these embryos cease to be preserved.

In addition to their essential object of regulating human behaviour and human interaction in everyday life, laws contain an educational dimension reflecting the way in which our society applies the values which are its foundation and therefore are a reference for these values.

The law states that, in specific circumstances, it is allowable to destroy a human embryo created *in vitro* in the context of an ART procedure, but which will not be transferred. But using embryonic cells for research purposes once the embryo has been destroyed would be a major transgression and should therefore be prohibited.

Prohibition would therefore seem in this case to relate not to the deed itself, i.e. destruction, but the fact that it may, or may not, be the source of research leading to scientific progress.

The contradiction was even more pronounced in the 1994 bioethics law, since the destruction of human embryos *in vitro* was authorised in some of the situations mentioned above and research was prohibited without exception.

CCNE remarked on this contradiction in the conclusion of Opinion N° 53, dated March 11, 1997 on The establishment of collections of human embryo cells and their use for therapeutic or scientific purposes: “We are approaching paradoxical situations as a result of legislation: there is a ban on research which can be detrimental to an embryo *in vitro* and therefore on research which could destroy it, but it can be destroyed after it has been kept for more than five years.”

Concerning the issue of research using embryonic cells, **it is the destruction of a human embryo, for reasons unrelated to any thought of acquiring new scientific knowledge, which can open the way for the possibility of research, not the acquisition of new scientific knowledge which leads to destruction.**

Research and sharing new scientific knowledge have always represented an essential ethical value for CCNE. But there are ethical issues arising out of the methods used by research and the way in which knowledge and its applications will be implemented.

The fact that the community is concerned, and rightly so, by the possible applications of some scientific advances, does not signify that scientific research is, in itself, a radically transgressive activity, nor that any particular conduct would raise less ethical, moral and societal issues if it were decided that it would not be followed by, or would not be the occasion for research to acquire new scientific knowledge. Otherwise, there would be a kind of inversion of causality and temporality, with research appearing to come before the decision and the act of destruction of a human embryo, and thereby being made to bear the responsibility of that act and that decision⁴⁸...

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The fact that derogation to the prohibition of research is only possible if “it could lead to major therapeutic advances” reinforces the idea that it is research itself which raises a problem: the only possible research being one for which the application is already known. The derogation therefore is more concerned with the predictable (and desirable) application than with research as such (see below, chapter E).

Clearly, **the desire to acquire new scientific knowledge may raise ethical issues when the research itself is the cause of conduct which raises ethical issues: this is the case in particular of research *on surplus human embryos in vitro* before their destruction, once destruction has been decided because the parental project has been abandoned (see chapter III), and *a fortiori*, the case of the creation of human embryos for the specific purpose of research** (see chapter IV).

Just as clearly, as mentioned above, any attempt to acquire new scientific knowledge can raise ethical issues because of the way it is carried out or because of its possible applications.

But considering that seeking to acquire knowledge would, in itself, raise a major ethical issue has consequences of an entirely different kind. **It is arguable that refusing to acquire new knowledge from a conduct seen as legitimate, is in itself an ethical issue.**

C. The prohibition on research also applies to embryonic cells which have already been isolated and cultured *in vitro*.

Most of the research on embryonic stem cells done in France so far, in compliance with the 2004 law, did not involve isolated cells from surplus embryos destroyed in this country after an ART failure. It mainly involved — by virtue of the derogation from prohibition provided by law — cell line cultures isolated from embryos that had been destroyed several years ago in other countries, but in circumstances corresponding to those required in France for the destruction of embryos conceived in the context of ART and for which the couple concerned had given free and informed consent to the cells being used for research purposes.

The prohibition in this case therefore bears on using, for research to acquire new scientific knowledge, cells which were isolated and cultured in a test tube, sometimes for quite a long time.

The same prohibition problem arises when cells were already isolated from a human embryo destroyed in France and had already been used, by derogation, for a specific research project. **Once that particular research project has been performed, any other research on cells already isolated and cultured *in vitro*, will remain prohibited, unless further authorisation to derogate is given.**

These provisions are the results of **lawmakers' general concern that embryos should not be subject to any form of reification.**

But, **to prohibit — with the possibility of derogation — any research on cells which are already isolated and cultured *in vitro* cannot but suggest that it is specifically research on those cells, which is viewed as transgressive.**

Is there a major ethical issue arising out of new knowledge-seeking research based on cells with an embryonic origin? And conversely, would refusal to seek new knowledge based on the study of these cells, which are already isolated and in culture *in vitro*, be an expression of retrospective respect for a human embryo?

Are we encountering here the application of a general principle, or does this approach only apply in the case of human cells with an embryonic origin?

D. Ethical reflection on an exception.

After elective termination of a pregnancy or a therapeutic termination, the law authorises cells to be isolated from the human embryo or the destroyed foetus and research using these cells, as prescribed by the general provisions applying to research on human cells, subject to informed absence of maternal opposition, specific consent not being required.

When human foetal cells have already been in culture for a period of time and subject to their having been isolated in accordance with the stipulations outlined above, **authorisation to perform research on these cells,** as on any other human cell, depends on an evaluation indicating that the research project is bona fide but is **not conditioned by derogation from a prohibition — contrary to the case when isolated cells originated in a destroyed *in vitro* human embryo.**

Much more generally, apart from the case of embryonic cells, **there is no prohibition on research involving human cells once their isolation and culture *in vitro* has been authorised.**

Human embryonic stem cells are therefore an exception.

Why should there be such an exception?

- **The reasons might be connected to the isolation procedures used for embryonic cells.**

The prohibition on research using cells isolated after the destruction of a human embryo could of course express the idea that it is not research on these cells as such which is seen as a major ethical issue, but the isolation of the cells when the embryo was destroyed, or rather the fact that special destruction modes could be used because of the decision to isolate the cells. Conversely, simply ceasing conservation together with prohibition of research, would lead to the spontaneous disappearance of the human embryo without any cell sampling action.

And yet, it should be noted that the law makes no recommendations on the way in which the preservation of human embryos should be regulated. **In other words, neither destruction itself, nor any particular method of destruction, and not even cell sampling and isolation are prohibited: the only ban is research on the cells.**

- **Another possible reason** for the existence of such an exception **is the special properties of certain human embryonic stem cells, in particular their initial totipotency in the earliest stage of embryo development.** It is true that the *totipotent* cells can, if they are isolated from the embryo, give birth to a human embryo.

However, the law already bans (without any possibility of derogation) the creation of *in vitro* human embryos for the purpose of research. It could not only forbid the creation of human embryos *in vitro* for research purposes, but also forbid the isolation and culture of *totipotent* cells. If that were the case, only *pluripotent* embryonic stem cells, those which appear after several days of embryo development *in vitro*, could be isolated and cultured. (However, see below, chapter VI, for a discussion of the more general implications, in ethical terms, of such an approach).

But it is not only this prohibition of research on embryonic cells which constitutes an exception; this is also true of the particular kind of derogation allowed for this prohibition.

E. The ethics of research and the therapeutic end-purpose of research.

1. “...The research could lead to major therapeutic advances”

The 2004 law on bioethics states that “...research on the embryo and embryonic cells may be authorised when it could lead to major therapeutic advances and on the condition that there is no alternative method of comparable efficacy in the present state of scientific knowledge which could be used instead; [...] the decision is taken with regard to the scientific pertinence of the research project, the conditions in which it is conducted in the light of ethical principles and of its usefulness for public health.”

Several of these conditions may appear to be redundant: to begin with, it seems obvious that research cannot “lead to major therapeutic advances” unless it is “scientifically pertinent. Furthermore, if it is likely to “lead to major therapeutic advances”, this would seem to justify a priori its “usefulness for public health”. In fact, this accumulation of conditions which are partially redundant seems to have the effect of suggesting the entirely exceptional nature of a derogation to banning such research.

On a scientific and medical level, restricting such derogations to only research which could “lead to major therapeutic advances” could, paradoxically, have the effect of slowing down the progress of research — including possible therapeutic discoveries. If it had been decided to limit genetic research in the fifty years which followed the discovery of DNA to the sole approaches which seemed at the time foreseeable and useful for gene therapy, this research would probably never have achieved the breakthroughs in scientific knowledge and unpredictable applications that we have been witness to. It could have been viewed, paradoxically, by the community, as research which was increasingly difficult to justify since it was solely connected to the exclusive expectation of gene therapy applications which, in fact, are only now, after half a century, beginning to demonstrate their feasibility.

Restricting the derogation to research on embryonic stem cells to solely the kind that is likely to “lead to major therapeutic advances” can also cause the public to entertain false hopes⁴⁹ because of the degree of emphasis given to therapeutic promises^{50, 51}.

“No, a thousand times no,” said Pasteur, “there is no such thing as a scientific category for which ‘applied science’ is an appropriate name. There is science and there are scientific applications, bound together as are the fruit to the tree which bore them. Society is often tempted to only consider the fruit and ignore the tree. And yet, so-called fundamental or cognitive research and so-called applied or finalised research are both essential, and one is not reducible to the other⁵².”

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In its Opinion N° 109, dated February 4, 2010, on *Society and the communication of scientific and medical information: ethical issues*, the Committee warned on the danger that “...Some of these statements may give rise to false hopes or disillusion and magnify some of society's doubts on the role of scientific research, in particular medical research.”

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One of the most scandalous (and retrospectively absurd) expressions of such representations may be remembered. South Korea issued a stamp after scientific publications (which later turned out to be fraudulent) in *Science*, authored by Hwang Woo-suk in 2004 and 2005, describing the (fictitious) procurement of human pluripotent embryonic stem cells *in vitro*, obtained from embryos created *in vitro* by nuclear transfer. The stamp pictured a paralysed person emerging from a wheelchair with a scientist (or a doctor) standing by holding a test tube (or a medical syringe)!

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When the law suggests that it is possible to select, and therefore to undertake as of now, research which could lead to major therapeutic advances, the idea is entertained that such treatment improvements are expected very shortly. Today's messages focus essentially on the possibility of *regenerative treatment* by grafting stem cells for a whole collection of serious disorders characterised by the anomalous disappearance or malfunction of certain cell populations. Paradoxically, by giving, at this early stage, *therapeutic* status to these embryonic cells and suggesting that such status is on its way to fast becoming reality, society can only envision a very near future in which such *curative cells* would need to be available in very large quantities in order to keep up with medical needs. To some extent, there is an implicit understanding that we should embark immediately on a course involving the forthcoming destruction of a very large number of embryos in order to respond to therapeutic promises now being made.

The object of this comment is in no way to prejudge whether this will or will not be the case.

But it should, quite simply, be repeated once again that research is above all a search for new scientific knowledge and that, if it should happen that therapeutic applications emerge from such research, they might be entirely unrelated to simply using embryonic cells for “medication”. In other words, today's research on embryonic cells cannot forecast in any way possible “requirements” for embryonic cells in tomorrow's medical world.

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It could be remarked on this point, that CCNE has on several occasions, but in a non exclusive manner, connected its recommendations regarding authorisation for research on embryonic stem cells or research on embryos, to the question of the therapeutic interest of such research. For example, in *Opinion N° 8*, dated December 15, 1986 on *Research and use of in-vitro human embryos for scientific and medical purposes*, the point is made that research should “take into account how it can improve therapy” and further on, “...the value and medical interest of a research project must also be taken into consideration”. In *Opinion N° 53*, dated March 11, 1997 on *The establishment of collections of human embryo cells and their use for therapeutic or scientific purposes*, the point is made that “the use of embryonic stem cells must be limited to fundamental research activities

2. “Measuring the worth of a scientific project by the yardstick of the intensity of surprise it generates.”

Research on stem cells, be they embryonic, foetal, neonatal (from the umbilical cord), or adult in origin, is in a state of turmoil which is part of a more general upheaval in the field of the life sciences.

What do we know about stem cells? Are they “immortal” as is often said, or rather are they cells which are capable of asymmetric division, which age and then die, but are capable of giving birth to younger and more fertile cells, which in turn age and die, as is the case for instance for ancestral stem cells like yeast cells? What mechanisms control the survival, ageing and death of stem cells?

The relation between stem cells and embryonic development, their connection to the ageing of the body and its capacity for repair, their link with cancer, are other essential issues.

On all of these subjects, research has already begun to overturn our knowledge and tenets and could lead to future therapeutic avenues which are unpredictable today and which could go infinitely further than the only horizons of which we are aware at this point, that is the injection of curative stem cells for “regenerative” purposes.

The pursuit of knowledge — which could be viewed as the true purpose of research — **and the possibility of attempting to develop possibly beneficial applications** — which could be viewed as one of the uses of research — **are deployed in two different time spans.**

When useful applications become possible, their development becomes a priority, but it is illusory and dangerous to believe that future applications will emerge from anything but the fundamental exploration of the unknown and unceasing questioning of the apparently already known.

François Jacob wrote: “the worth of a scientific project can almost be measured by the yardstick of the intensity of surprise it generates. [...] The really interesting part is the one which is unforeseeable⁵³.”

or therapeutic research...”. And in *Opinion N° 67*, dated January 18, 2001, on *The preliminary draft revision of the laws on bioethics*, CCNE speaks of “*therapeutic research projects*” and of “*research for medical purposes*”. Thus, while legislators did not choose to follow CCNE’s recommendations for conditional authorisation of research on embryonic cells, research on the embryo and (by derogation from prohibition) the creation of embryos for research in the context of the evaluation of new ART procedures, they did — to a very restrictive degree — follow CCNE’s recommendations in the specific field of the therapeutic implications of research.

“There is a category of people for whom the unpredictable character of research is hardly tolerable, namely politicians and administrators of science, who are wary of projects that lack a precise goal.”

“Yet science is also unpredictable. Research is an endless process and we can never say how it will evolve. Unpredictability is of the essence of scientific enterprise. If what we are going to find out is really new, then by definition it must be something we cannot know in advance.”

(François Jacob. *Of Flies, Mice and Men*. Op. cit).

From this ensues also the frequently totally unexpected nature of the applications to which it may give rise. It is quite possible that some research on embryonic stem cells with no currently foreseeable therapeutic applications, could dramatically alter the state of the art and lead, at some future time, to entirely unexpected therapeutic breakthroughs.

Obviously, any research can raise ethical issues and should therefore be subject to meticulous evaluation of the way in which it is carried out and its possible applications.

As regards research on stem cells, in particular human embryonic stem cells, in its *Opinion N° 93*, dated November 11, 2006, on the *Commercialisation of human stem cells and other cell lines*, CCNE insisted on the importance of giving thought to patents and licenses, and on the need to make sure that commercial considerations do not lead to limiting access, for the world's less fortunate inhabitants, to the possibly useful applications for health of such research.

A further paradox is worthy of note: although a derogation to the prohibition on research involving embryonic stem cells requires it to be capable of leading to major therapeutic progress, so far none of the institutions implicated in the regulation of therapeutic trials — be it AFSSAPS (the French Health Products Safety Agency), the Agence de la Biomédecine, DGS (Direction Générale de la Santé/ Public Health Authorities), etc. — has responded to even one of the requests made by a French research team to initiate clinical research for the purpose of evaluating in humans the efficacy of new treatment, based on the use of cells derived from embryonic stem cells, for any particular disease for which there is, to date, no effective alternative treatment.

F. The ethics of research and the process of free and informed consent.

All too often, there is a tendency to forget that **there can be no research based on human embryonic stem cells unless the couple concerned gives free and informed consent to the procedure.** In other words, if no couple consents to such research — if every couple refuses — the very question of such research being undertaken disappears altogether. The law is such that the couple's decision in this respect is a necessary, albeit not sufficient, condition for research to take place.

CCNE has always insisted on the vital ethical importance that must be given, as regards research, to the quality of free and informed consent procedure. Anything which might weaken or limit its scope would be detrimental to the ethical quality of the research process.

This is the reason why must be examined the details of the free and informed consent procedure proposed to the couple who have explicitly made known the ending of their parental project. (In the event of implicit termination of the project, i.e. no response after five years have elapsed, the embryo is destroyed and no research is permitted).

At least three points concerning the free and informed consent procedure provided by the 2004 bioethics law merit consideration.

- 1. One single consent (or refusal) for research *on cells isolated after the embryo's destruction* and for research *on a live embryo before its destruction.***

The law has put research on a live *human embryo* and research on human embryonic *cells* on the same footing, under the one heading of “*research on embryos and embryonic stem cells*”.

The two situations have therefore been dealt with in the same way (although they raise different kinds of ethical issues, see below, chapter III).

As a result, a couple can only consent to research in terms of ‘all or nothing’: if they consent to research, it may involve isolated *cells* sampled from the destroyed embryo, but could just as well involve a live *embryo* before destruction.

The law does not allow the couple to accept only research on cells but not on the embryo. In other words, **the information given to the couple presupposes *a priori* that consent to research is equivalent to consent for research on a live embryo.**

This ambiguity in the free and informed consent procedure is expressed in the actual formulation of the choice: the law says that the couple can consent to their embryos being the subject of research *or* [and the emphasis is ours] that they cease to be stored. Obviously, the ‘*or*’ becomes highly significant when research concerns live *embryos*, before their destruction.

When, however, research involves isolated cells sampled from the destroyed embryo, the ‘*or*’ should be replaced by an ‘*and*’: consent (or refusal) should be for ending storage of the embryos, *then* (therefore ‘*and*’) the cells taken from the destroyed embryos would be the subject of research.

2. The connection between ethical evaluation of research and consent to research is in reverse order to the usual procedure.

When, in biomedical matters, the possibility of research is subject to a free and informed consent procedure, the first step is evaluation of the research by one single (or several) scientific and ethical body or bodies. It is only if the research is judged to be both scientifically legitimate and ethically acceptable that free and informed consent procedures are initiated.

In this case, the free and informed consent procedure is submitted to the couple before the research project is considered by the *Conseil d’orientation de l’Agence de la Biomédecine*, which carries out an ethical evaluation after receiving the scientific evaluation provided by a group of experts the Agency had designated.

It is therefore the principle of research itself which is in this case the subject of the free and informed consent procedure submitted to the couple, and not the specific research project which will be undertaken if consent is given.

It may be supposed that the already exceptional nature (see above) of the *a priori* restriction on research which will be authorised only if it “would be capable of leading to major therapeutic progress” is a form of information on at least the purpose of research, but it does not inform, contrary to what is usual, on the nature and object of research. Be that as it may, the information is incomplete.

In its Opinion N° 93, dated November 11, 2006 on the *Commercialisation of human stem cells and other cell lines*, CCNE suggested that another form of information should also be given to the couple enabling them to choose when the research project involves human embryonic stem cells: not just information on the nature and object of research, but also on the economic model governing the project, in particular whether applications would be developed for profitmaking or non-profitmaking purposes, whether a patent would or would not be filed and, if a patent were to be filed, whether provisions would be made, or not, to avoid excluding access to applications by the underprivileged.

The inversion of the customary sequence — a scientific and ethical evaluation procedure, followed by the free and informed consent process — also has the consequence that it sets no time limit on the conservation of embryos after termination of the parental project and consent is given to research by the couple concerned.

It follows that this particular situation does have the effect of improving the quality of research since it means that a research project would not be undertaken until the time comes when, and if, are met all the criteria for it to be authorised.

But such conservation without any upper time limit, potentially indefinite, between the abandonment of the parental project and the possible time when some future research project is undertaken, represents in fact a considerable change in the way in which the ethical issue of the embryo's fate is approached. In this situation, the embryo can now be cryopreserved for an indefinite time solely *for the purpose* of research⁵⁴.

3. Free and informed decision and research "capable of leading to major therapeutic advances".

The exceptional character (compared to all the other research projects subject to the free and informed consent procedure) of the mandatory conditions required when embryonic cell research is involved, plus their required evaluation by the *Agence de la Biomédecine*, before the parental couple are asked for consent, could suggest to the couple that in this case, unlike

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These thoughts give rise to three comments, which are related to the discussion above concerning research on embryonic *cells after destruction* of the embryo or *on live embryos before they are destroyed*.

The first comment is that embryo cryopreservation while awaiting the possibility of a research project should only be considered if the couple gave consent to research *on the embryo*.

The second is that, in this case, it would be appropriate to propose a time limit on embryo conservation.

The third comment is that if the couple could choose between giving specific consent only to research on isolated *cells* sampled from the destroyed embryo, it would not be necessary to continue embryo cryopreservation. Conservation could be brought to an end and isolated cells from a destroyed embryo could be put into cryopreservation without any ethical issue arising out of a possible time limit.

As already mentioned above, it would only be in the event of a couple consenting to research *on the embryo* itself that there would be a true alternative — a real 'or' — to ceasing conservation, with this alternative including the temporal dimension of prolonging cryopreservation. Consent to research on the embryonic *cells* would correspond to an 'and', that is stopping conservation of the embryo and then isolating cells from the destroyed embryo.

the situation for all other kinds of research, society may be making a commitment that the research could lead to the development of treatment for patients.

There is therefore a risk that the couple's free and informed consent to research will be guided in the direction of acceptance, because the necessarily uncertain nature of the results of any form of research will be somewhat obscured, and the impression will be given that it is not so much a question of *searching* to acquire new scientific knowledge as of *finding* treatment. As a result, there is a probability of bias in favour of parental consent.

This is a paradoxical situation which needs thinking about: not only is there a time inversion, as noted above, in the usual sequence of an independently generated scientific and ethical evaluation of the research project, followed by submission of the project for free and informed consent, but there is also a **prior bias given to the first and necessary condition for such research to be possible, i.e. parental consent, and an accumulation of an extremely restrictive set of subsequent conditions, although their objective's feasibility is less credible than the expression of their severity.**

G. Conditional authorisation or derogation from a prohibition? Ethical reflection on legal formulations.

1. The destruction of human embryos is the primary ethical issue, not the decision to perform research on cells *after* embryos are destroyed.

The possibility of research on isolated cells sampled from an embryo which was destroyed because the parental project has been abandoned, or in the course of a PGD procedure, has no influence whatsoever on the decision to destroy the embryo. It happens later.

In other words, **in no way does the possibility of research have an effect on the decision to destroy the embryo.**

Prohibiting research does not protect human embryos from destruction.

The primary ethical issue, therefore, is the destruction of human embryos.

The legal formulation chosen by lawmakers to define this approach, that CCNE described as being as a '*lesser evil*', is (as CCNE has always recommended in all of its Opinions) is a '*conditional authorisation*'.

The question of possible destruction of spare embryos, in the event of the termination of a parental project, **in fact arises at an earlier time,** when they are created and stored⁵⁵. **The creation and cryopreservation of these spare embryos is not a systematic procedure** and is only actually implemented, once the parents are informed and have consented, for 25% of

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So as to enable a new attempt at embryo transfer if a pregnancy fails, or a new parental project after the birth of a previous child without having to undergo more hormonal hyperstimulation and further ovarian puncture.

couples resorting to ART and IVF⁵⁶. Some opinions are in favour of more detailed prior information on the future of spare embryos to be given to parents before creation and conservation takes place⁵⁷.

Some bodies of opinion consider that this formulation of conditional authorisation for the creation, conservation (and therefore also destruction) of embryos in the context of an ART procedure, as it is currently expressed by law, is not sufficiently emblematic⁵⁸.

Should we consider that the destruction of spare embryos in the context of a PGD procedure should be expressed in the form of a derogation to a prohibition?⁵⁹

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Currently, cryopreservation is only implemented for 25% of couples resorting to ART and IVF procedures. In Audition of Mme Jacqueline Mandelbaum, p. 83 of *Rapport d'Information n° 2235, drawn up in the name of the Mission d'information sur la révision des lois de bioéthique, Assemblée Nationale (Chair: Alain Claeys, Rapporteur Jean Leonetti)*, January 2010.

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This is what was proposed at the Estates General on Bioethics in 2009: We would also consider it highly desirable that detailed information be given at this time to intentional parents and that they should be asked at the outset to take a decision on what should be done with superfluous embryos should they not respond to enquiries at a later date (destroyed, given to another couple or donated for research purposes). Report by the *États Généraux de la Bioéthique. Annex 9. Contributions from Regional Forums. Citizen opinion given by the Marseilles panel. Estates General on Bioethics*. (For more exhaustive extracts from this Opinion, see Chapter V.II).

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And that it is precisely this symbolic weakness regarding the destruction of the embryo *in vitro* that led lawmakers to provide for — as a form of compensation — a supplementary symbolic burden *elsewhere*, in this case on research using cells from the destroyed embryo.

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But then should be taken into consideration the risk of aggravating an already frequent feeling of transgression, or even of guilt, on the part of couples resorting to ART, and to a greater degree PGD, who are already acting as a consequence of distress, due to infertility on the part of the former, and to the suffering due to the unfortunate appearance in their family of particularly severe incurable disease, for the latter. It would also seem important with such an approach, to separate ethically the case of the creation and preservation of spare embryos, which is a prior condition to the possibility of their destruction, from the case of the destruction of embryos in the context of PGD, since the two ethical situations are very different.

CCNE has always distinguished between the two and considered the possibility of reducing future recourse to preservation of spare embryos, so as to limit the possibility of their destruction, without including in this approach the issue of destruction of PGD generated embryos. For example, see on this subject, *Opinion N° 67*, dated January 18, 2001 on the *Preliminary draft revision of the laws on bioethics*: “CCNE points out, however, that the number of spare embryos which could be available for research is likely to decrease in the future because of improved technical skills, and because of smaller numbers needed on average for embryo transfer on each occasion. Care should therefore be taken to make sure that medically assisted reproduction is not used to voluntarily stock up on spare embryos so as to be able to use them later for research”.

The main ethical issue is perhaps discovering whether society as a whole would be ready to stand by the principle of forbidding the creation, preservation and possible destruction of spare human embryos, thereby expressing the respect owed to human embryos, and of a derogation to this prohibition, under specific conditions. The derogation would be seen as representing the ‘*lesser evil*’.

2. The various possible meanings of a derogation from a prohibition.

Article 16 of the *Code Civil* states that the law “guarantees respect for human beings from when life begins⁶⁰.”

But the law also authorises putting an end to conservation, and therefore also the destruction of spare embryos in cryopreservation when they are no longer included in a parental project, as well as the destruction, in the context of PGD, of those embryos carrying the genetic defect which was the object of the PGD procedure.

In fact, the law’s formulation on this point agrees with the *Conseil Constitutionnel*’s opinion (in its July 27th 1994 decision) in which it stated that “legislators had provided a large number of guarantees regarding conception, implantation and preservation of fertilised embryos in vitro,” but “had not considered it necessary to ensure the preservation of all already formed embryos for an indeterminate period of time and in every possible circumstance.”

Be they spare embryos, or embryos carrying the genetic sequence under investigation in the context of PGD, **the destruction of human embryos does in fact correspond to an exception from the provisions of Article 16 of the *Code Civil*.**

And yet, lawmakers did not regulate this procedure in the form of derogation from a prohibition; it appears as a conditional authorisation.

In *Opinion N° 8*, dated December 15, 1986 on *Research and use of in-vitro human embryos for scientific and medical purposes*, CCNE wrote: “The de facto situation resulting from the production of a larger number of embryos than can be medically transferred raises questions that we should try to answer. However, solutions proposed in the present opinion do not legitimate this de facto situation. Such solutions are, therefore not final: one can envisage and hope that, in the future, research will allow fertilisation only of the necessary oocytes for transfer for the birth of a future child”.

But almost a quarter of a century later, CCNE noted in *Opinion N° 107*, dated October 15, 2009 on *Ethical issues in connection with antenatal diagnosis: Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD)* that research in this respect had not made significant progress and that the “live birth success rate after oocyte retrieval is around 20% and there is little likelihood of this figure improving in years to come since it is in fact quite close to the figure for natural conception”.

Article 16 of the *Code Civil* situates this measure in a much broader context: “The law ensures the primacy of the individual, prohibits any encroachment of to the individual’s dignity and guarantees respect for human beings from when life begins.”

In this case at least, **lawmakers viewed formulation in the shape of *conditional authorisation* as equivalent — or rather preferable — to *derogation from a prohibition*.**

But there are other cases where these two formulations of derogation from a prohibition and conditional authorisation do not have the same significance.

***Derogation from a prohibition* may in fact have at least two other very different meanings.** In other words, there are at least two very different kinds of conduct regulated by using this same formulation:

- For one first category, **derogation does not cover a specific exception to a prohibition, but rather a conduct whose conditions for implementation and objectives are specifically defined** ⁶¹.
- For a second category of conduct, **derogation from prohibition** is entirely different: **it consists in making certain that the derogation remains an exception, the derogation itself being a transgression which must be limited through case-by-case regulation to the maximum extent possible.**

While the first form of derogation can be viewed as very much akin to conditional authorisation, this is absolutely not the case for the second⁶².

It is worth noting that if the same derogation from prohibition formula is used to describe indiscriminately both the first and the second category of conduct, it is difficult to avoid the possibility of confusion.

Probably for that very reason, CCNE chose in its recommendations:

- to use the expression ***conditional authorisation*** to describe the act of **destruction of spare human embryos** no longer included in a parental project (and to characterise research on embryonic cells or on the embryo in this context), which the CCNE defined as a regulated ‘lesser evil’;
- and to use the expression ‘***derogation from prohibition***’ to characterise a **totally different course of action**, that it saw as **an exception** which could only be considered on a **case-by-case** basis, and as a **transgression from the prohibition** to

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This is the case for example, in an entirely different context, of surgery which is defined by law as a general derogation from the prohibition of prejudice to the integrity of the human body. Clearly, this derogation from a prohibition does not aim to put on surgeons the burden of responsibility for a transgression, nor to restrict *a priori* the number of derogations so that they become exceptions. Mention of the prohibition takes on in this instance a strong symbolic value, with the object of emphasising the importance attached to the concept of respect for the integrity of the human body.

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But in any event, it is important that derogation from prohibition is not mistaken — which happens all too often — with a negation or an abolition of the prohibition as such. Derogation is always an attempt to solve an ethical conflict between different values, principles or essential rights which, in some specific situation, are at variance.

create embryos for the purpose of research: **embryo creation for research in the context of an evaluation of new medically assisted reproduction techniques**⁶³.

Therefore, while a derogation always has the effect of calling attention to a prohibition, and a reminder concerning a prohibition is always highly potent as a symbol, the significance of a derogation and of the behaviour which that derogation authorises, may not be immediately obvious and may need clarification to be completely understood by the community.

CCNE expresses the wish that action be undertaken to **harmonise, in the large number of laws bearing on biomedical ethical issues, the respective uses of the expressions ‘conditional authorisation’ and ‘derogation from prohibition’** in cases where they seem to apply to similar situations. With such harmonisation it would be possible to attach an appropriate degree of value to the formulation of ‘derogation from prohibition’, to prevent its trivialisation, to assist society in a better understanding of the ethical issues involved, and to reserve its use for exceptional circumstances which raise very specific ethical quandaries, those which are the most important and the most difficult to solve⁶⁴.

While the thought was never formulated in those terms, it could be inferred from CCNE’s past Opinions taken as a whole that it has always considered that the two circumstances in which it sees as inevitable the destruction of non implanted embryos created *in vitro* in the context of ART are, firstly the case of spare embryos after the parental project has been abandoned and no other infertile couple wishes to take them on and, secondly when in the course of PGD, the genetic defect which motivated the PGD procedure is detected. But although destruction may be inevitable, this does not mean that it is ethically satisfactory, which CCNE translates in ethical language as the *lesser evil*.

In this Opinion, the ethical approach should include all of the following:

- affirmation of respect for human embryos as “potential human beings”,
- recognition at least that there is a great deal of perplexity on how to define the status of embryos,
- and the contingent acceptance of the possibility that their integrity may be breached in particular circumstances, depending *inter alia* on whether they can, or cannot, be included in a human relationship, a parental project which is a necessary condition for their future existence.

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Opinion N° 8, dated December 15, 1986 on *Research and use of in-vitro human embryos for scientific and medical purposes* and *Opinion N° 67*, dated January 18, 2001 on the *Preliminary draft revision of the laws on bioethics*.

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As regards the destruction of embryos *in vitro*, after the parental project has been abandoned, and research on cells from these destroyed embryos, as mentioned above CCNE has always considered that the *most appropriate legal formulation* to take account of the complexity of the ethical issues involved, was neither *simple authorisation* nor *derogation from prohibition*, but rather conditional authorisation.

It would be in such a context that could be entertained, “**compromises made tolerable by the ethical principle of the lesser of two evils**”⁶⁵,” as formulated previously by CCNE.

CCNE wishes to emphasise the importance of seeking such compromise solutions⁶⁶, not because of being unable to choose but, on the contrary, out of choosing a behaviour that is reasoned, that can be acceptable to others, that refuses to cling to certainties, and that takes fully into account the complexity of the “potential human being” enigma and grants full pride of place to the parental project which registers the human embryo, even before its creation, as a part of a human relationship which is the very condition for its future existence.

III. Research on human embryos developing *in vitro* (embryos created as part of an ART procedure but not transferred): ethical reflection in the context of the 2004 law on bioethics.

A. From the issue of research on cells isolated after destruction of the embryo *in vitro* to the issue of research on the embryo *in vitro* before destruction.

Be it for research on cells isolated from an already destroyed human embryo or research on a human embryo before its destruction, **research was not the cause of the embryo’s destruction in either case. The cause of the embryo’s destruction is the fact that it will not be transferred**, either because the parental project is no longer current (in the case of spare embryos) or because the embryo is carrying the genetic sequence which is related to an incurable and particularly severe hereditary disease (in the case of PGD).

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Opinion N°8 dated December 15, 1986 on “*Research and use of in vitro human embryos for scientific and medical purposes*”.

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This compromise would need to be formulated in legal terms:

- either following CCNE’s previous considerations with a view to using the legal formulation of ‘conditional authorisation’, an approach that was validated by the Conseil d’Etat,
- or by adopting a legal system of ‘prohibition with possible derogation’, so as to give the greatest exposure to the potential human life symbol, and adding an explanation of the ethical issue,
- or by drafting a new legal formulation, if it is thought that:
 - the ‘conditional authorisation’ system would not be sufficiently potent as a symbol,
 - the ‘prohibition with derogation’ system would be too emphatic, in particular in view of other legislation on bioethics.

CCNE hopes that the formulation adopted by law will include a fully explicit description both of the concept of authorisation and that of the *lesser evil*.

In both of these cases, the decision to carry out research, if it is taken, will therefore come after the decision to destroy the embryo and will have had no bearing on the decision to destroy.

Nevertheless, these are two very different situations.

In the first case — research on cells — research takes place *after* destruction of the embryo, on embryonic cells. In the second case — research *on* the embryo — it is a living embryo, in the process of development, which will be the object of research *before* destruction. And the research itself, although it is not the cause of destruction, raises an ethical issue.

B. The concept of embryonic *development* and the issue of the maximum time allowed for *in vitro* development.

All living entities are always more than, and always different from, their constituent parts. This is true in scientific and biological terms⁶⁷, but also on other levels, in particular philosophical or ethical. If the embryo is not transferred, carrying out research on an *in vitro* embryo *before* destruction does not raise the same ethical issues as carrying out research on the cells from that embryo *after* destruction. In the first case, research will be taking place on a living and developing human being — an incipient being, even if the decision to interrupt that future has already been taken. In the second case, research will be carried out on living cells removed from a destroyed embryo⁶⁸.

Lawmakers, with regard for the protection of human embryos, have put research on a *living embryo* and research *on embryonic cells* on the same legal footing.

And this approach has at least three implications.

As stated above, the first two implications concern the nature of the free and informed consent given by the parents in the event they are not pursuing their parental project. And it would be advisable that:

- on the one hand the couple should be able to choose specifically to consent to research on isolated cells from the destroyed embryo without necessarily having to also consent to research on the live embryo before destruction⁶⁹;

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“The whole is greater than the sum of its parts”, said Aristotle. This is true of a living being but also of an organ: for example, a line of nerve cells isolated from a brain is not the equivalent of a brain.

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The specific case of *totipotent* cells has already been referred to above (chapter II.G).

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- and on the other hand, in the event of consent to research on the living embryo before its destruction, a maximum lapse of time allowed for cryopreservation before research begins should be specified.

The third implication does not concern the parenting couple's consent, but the actual future of the human embryo.

Although the legal system is identical for a living human embryo developing *in vitro* before destruction and for cells sampled from an embryo that was destroyed, the law does not stipulate a time limit for any research which might be undertaken using a living human embryo: theoretically, such research could be carried out as long as the *in vitro* embryo's development is (or will be in future) technically possible. There is nothing in the law as it is currently written to prohibit this from taking place.

In Great Britain, on the contrary, where research on human embryos *in vitro* is authorised under certain conditions, any research on the embryo is strictly prohibited after a certain time has elapsed, i.e. a maximum of fifteen days of *in vitro* development of the embryo, this being the stage where nerve cells appear⁷⁰.

More than once, CCNE has emphasised the importance of this concept of temporality, not as a function of the stage of differentiation of the embryo (as was the case in Great Britain), but rather as a difference between the pre-implantation phase and the phase when the embryo becomes capable, if the decision is taken to transfer, of implantation in the mother's body, i.e. a maximum of 7 days. **CCNE recommended that in the event of research on the *in vitro* embryo, the *in vitro* development of the embryo should not be allowed to continue beyond this maximum time of a week⁷¹.**

And conversely, since generally the research differs in both type and object.

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The ethical reason for this time lapse is identical to the one which led Britain to authorise research conditionally not only on embryos created in an ART context and which will not be transferred (because the parental project has ceased to exist or because of a diagnosis in the context of PGD) but also the creation of embryos *in vitro* for the sole purpose of research (be that by fertilisation or by nuclear transfer) and which must be destroyed within the maximum time lapse of 15 days. The ethical considerations in Britain were the following: because it is the cessation of any detectable cerebral activity — brain death — which currently defines death in legal terms, and therefore the passing away of the human being, absence of the emergence of the brain defines the absence of the human being's inception. The maximum time of 15 days of *in vitro* development corresponds to the appearance of the very first events of cellular differentiation which will later lead to the emergence of a nervous system.

This argument, which turns the beginning into a mirror image of the end, has the advantage of being extremely logical and entirely straightforward. But perhaps the beginning is more than (or at least different from) the simple mirror image of the end, and perhaps a promise is more than (or different from) the simple inverse image of regret...

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In *Opinion N°67* dated January 18, 2001, on the *Preliminary draft revision of the laws on bioethics*, CCNE suggests: "Allowing the development *in vitro* of a human embryo beyond the end of the pre-implantation

Whatever view one chooses to adopt, which will, to at least some degree, be arbitrary, **it would seem important** that this problem, which is specific to research on the living *human embryo*, be taken into account and, in particular, that a **maximum time limit be set by law for development *in vitro*, in view of the fact that this would be minimal mark of respect for the embryo as a *potential human person*, that is an *incipient* being.**

IV. A major ethical issue: the creation of human embryos *in vitro* for the purpose of research.

A. The creation of human embryos for the purpose of research and the reification of the human embryo.

The statement that the human embryo cannot be defined is in itself a call for ethics based on respect: **to treat human embryos as though they were merely instrumental to scientific experiment amounts in practice to deciding on their status as beings by integrating them into the order of objects.**

In Opinion N° 8 on *Research and use of in-vitro human embryos for scientific and medical purposes*, CCNE stated: “From the time it has been conceived the human embryo is a being and not a possession, a person, not a thing nor an animal. It should be considered as a would-be subject, as an “other” of which we cannot dispose and whose dignity defines limitations for the power or control of others.” Also that “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. [...] Such consideration should take precedence over the advantages that might result from using human beings as though they were objects, even though it represents potential for the improvement of medical knowledge and furtherment of science. Respect for human dignity must guide both the development of knowledge and the limits or rules to be observed by research.” And: **“Even with the consent of genitors, fertilisation should not be done for research purposes alone. If it were, human embryos would purely and simply be used as tools or objects...”**

And in Opinion N° 67, dated January 18, 2001 on *the Preliminary draft revision of the laws on bioethics*, CCNE **reiterated this rejection** and made a clear distinction between the question of research using embryos created in the context of ART and the question of the creation of embryos for the sole purpose of research⁷².

stage, is prohibited.”

“Mindful of the risk of ethical misuse which could result from the reification of the human embryo, i.e. considering it as a thing and no longer as a potential human being, CCNE has already make known its views regarding research on the embryo. On the substance, it agrees with choices made in the preliminary draft :

- on the one hand, **re-stating the principle whereby producing human embryos by in vitro fertilisation for research purposes is prohibited;**

B. An ethical conflict: respect for the embryo and the creation of embryos specifically for the development and evaluation of new ART procedures.

The ethical concern to refrain from creating embryos *in vitro* for research purposes could be in conflict with a medical ethical concern, i.e. do the best one can to avoid endangering an unborn child in the context of implementing a new technique intended to improve ART.

This ethical concern not to create embryos *in vitro* for research purposes could also be at odds with another ethical concern, that of developing new techniques aiming to improve ART, which could avoid having to create and cryopreserve spare embryos and thereby steer clear of the possible destruction of embryos if they are not transferred.

This question is connected, in particular, to the possible technical progress which could either lead to improving the results of IVF as regards the probability of a child being born following implantation, or to oocyte conservation (for example, using a new rapid cryopreservation procedure, called *vitrification*) so that in the event of ART failure, new IVF procedures could take place without needing to go through a another oocyte sampling phase.

These questions cannot be investigated based on research using spare embryos already in storage, awaiting destruction because the parental project is no longer current, since they were cryopreserved using the older ART techniques previously authorised and used in France (and still in use today).

Research is ongoing in several countries on these new techniques and, in some countries, are already viewed as being current medical practice. But, in the present circumstances, research cannot take place in France as before any transfer of such embryos could be considered, there would have to be embryo creation for the purpose of research, which is prohibited (without any possible derogation) by the 2004 law on bioethics.

CCNE has been deliberating for some time on how best to deal with this issue.

For instance, in *Opinion N° 8*, dated December 15, 1986 on “*Research and use of in vitro human embryos for scientific and medical purposes*”, CCNE wrote: “...one can envisage and hope that, in the future, research will allow fertilisation only of the necessary oocytes for transfer for the birth of a future child. Medical research should endeavour to reduce the number of cases raising ethical issues, rather than accumulate an ever-growing amount of problems of a degree of severity which is disproportionate to the intended objective⁷³.”

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- on the other hand, opening up regulated possibilities of research on spare embryos "which are no longer included in a parental project".

In this Opinion, CCNE was not in fact considering the creation of embryos for research purposes with a view to evaluating new ARTs. Nevertheless, it was considering the possibility of creating embryos in the context of a medical test for diagnosing fertility. It expressed, as mentioned above, the rejection of allowing the creation of embryos for research: “Fertilisation of oocytes for research is not possible. It would be contrary to the principle described above.”

In Opinion N° 67, dated January 18, 2001 on *the Preliminary draft revision of the laws on bioethics*, CCNE agreed “with the article [in the law as proposed], which calls for a compulsory evaluation of new medically assisted reproduction (MAR) techniques before they are implemented. This sensible step, which aims to prevent a repetition of previous errors, raises the issue of what happens to embryos which will inevitably be produced by in vitro fertilisation during these validation procedures, which appears to be a reasoned exception to the general principle of not allowing the production of human embryos by in vitro fertilisation for research purposes. The course chosen, which is the destruction of embryos used in evaluation protocols, is clearly fitting.”

And CCNE concluded Opinion n° 67 with the following:

**“ – a firm reminder of the principle that creation of human embryos for the purpose of research is prohibited;
- the introduction of an exception to this principle in the context of evaluation of new medically assisted reproduction techniques.”**

It is worth noting that, so far, many IVF technical advances have been arrived at for ART without the benefit of prior research, in particular as regards embryonic development before embryo transfer. It so happens, fortunately, that these medical procedures do not seem to have proved a significant threat to the health of children born with the assistance of such innovative techniques.

Ethical issues connected to the advances of ART deserve to be considered comprehensively. For example, apart from any prospect of research aiming to improve ARTs, the simple translocation to France, for medical implementation, of a new and improved ART, validated in a foreign country⁷⁴ without the benefit of authorisation for any prior clinical research to validate the technique on embryos that will not be implanted, raises an ethical issue as regards the protection of unborn children.

Furthermore, the existence of **a major problem in this respect** must be pointed out: none of the specialised agencies — *Agence de la Biomédecine, AFSSAPS, DGS*, etc. — are currently ready to pronounce themselves on whether the cryopreservation of oocytes, be it by the known slow freezing method or by more recent vitrification techniques (which have been implemented in ART procedures in several countries and have led to the birth of a large number of children) is to be related to research or to clinical practice.

In this context, it would be worthwhile to ask an independent body to carry out a medical, scientific and ethical evaluation of the criteria which would allow for the use in France of new ARTs which are already standard medical procedure in other countries.

But the Opinion did introduce the idea of a derogation specific to this prohibition: “It is, however, possible to envisage that oocytes could be fertilised with the husband's sperm (excluding cross fertilisation test) with a view to establishing a diagnosis. It is up to the couple to decide, with the doctor's approval, whether such embryos should be implanted, destroyed or donated for research purposes, exactly as if they were excess embryos. Such embryos are dealt with according to the rules described above.”

As regards the complex matter of the possible creation of embryos *in vitro* for the purpose of evaluating new ARTs, **the ethical issue in this instance is to question whether respect for human embryos and refusal to allow them to be instrumentalised should, or should not, be infringed in order to protect unborn children.**

But obviously, if the possibility of carrying out such research was considered, with the aim of evaluating the feasibility and safety of new ARTs, **such research projects would raise major research and medical ethics issues as regards the evaluation of their objectives and the risks involved**⁷⁵.

It can well be imagined that such approaches could relate to very diverse situations, for example the destruction of an embryo created with a new technique in the event of doubt on its development, or systematic implementation of a number of evaluations before transfer, with the possible consequence of destruction of the embryo *in vitro*. Between such possible approaches and the creation of embryos truly for the purpose of research in the broadest sense of the term, there would probably be a vast and particularly complex area of ethical debate.

V. Prospective reflection: ethical issues raised by research on non embryonic human stem cells.

Research advances on somatic cells of the adult body have been presented, perhaps in a manner bordering on the naive, as an ethical scientific solution to the ethical problems arising out of research on embryonic cells. **It is true that, by making the impossible become possible, science can provide solutions to ethical problems. However, this should not obscure the fact that, in so doing, scientific advances have often created new ethical issues.**

Scientific advances on iPS cells (see above, chapter I.G), that is converting adult somatic cells, for instance skin cells, into cells which are similar to embryonic cells, may in future raise ethical issues which would benefit from being considered now rather than later.

At this point, dedifferentiation of somatic cells in the adult body stops, without going through the embryo-forming phase, at the *pluripotent* phase, before the *totipotent* phase. There is, however, nothing in scientific data to indicate that dedifferentiation could not be pursued up to and including the *totipotent* step.

Would it be allowable to raise such a question experimentally, the positive response to which could only be obtained via the creation, for research purposes, of an *in vitro* embryo? And supposing this first experiment was successful, should it be prohibited to repeat it, knowing

⁷⁵If such research was being considered, it would require specific organisations and scientific, medical and ethical evaluation methods to be set up as part of the assisted reproductive technology context. In any case, if such research was to remain prohibited, resources of this kind would be just as essential, as mentioned above, to evaluate and consider transporting to France new ARTs which have been successful in giving birth to a large number of children in other countries.

that it is in fact the creation of an embryo, or should it be considered on the contrary that this is simply an experiment in cellular dedifferentiation which would not raise ethical issues of a similar nature?

Reflection on the possibility of such discoveries also leads to raising a more general and more complex issue, which can be outlined in the following way, reverting to start with to the “natural” embryo. The *totipotent* cells composing an embryo in the very first phases of its development are incapable of giving birth to a new embryo as long as they are included in the embryo they are constructing. However, when they are isolated from this embryo, depending on the *in vitro* environment provided for the *totipotent* cells, they will give birth to a new embryo or will become cells of one of the more than 200 families of body cells which cannot, spontaneously, give birth to an embryo.

In other words, it is the nature of the environment which is provided for them artificially *in vitro* which will determine the future of these cells; the environment can either unlock, or constrain, some of the cells’ potentialities.

But if, in the near future, it became possible to derive, depending on the environment provided for them *in vitro*, *totipotent* cells from the skin cells of an adult, should we prohibit, in retrospect and for ethical reasons, research on adult body cells in view of the discovery of their hitherto unknown *potential capacity* to give birth to an embryo? Or should we rather prohibit providing them with the environment which enables the creation of an embryo, that is forbid the creation of an embryo *in vitro*?

This is a complex issue, which brings us back to the ethical problem raised by the possible use of *totipotent* cells isolated from “natural” embryos (see above, chapter I.G.3, on the subject of *totipotent* embryonic cells). Should we, for ethical reasons, ban the process of isolation, because of the cells’ *potential*, or should we simply ban providing them with the environment which allows the creation of an embryo using these cells? And if, in the future, it became possible to obtain, depending on the environment chosen for them, *totipotent* cells from *pluripotent* embryonic cells, should we ban the isolation process, or simply ban their use for the creation of embryos?

More generally, we have here an alternative formulation for the ethical considerations which were discussed above when the concept of boundaries was being considered: should “ethical safeguards” refer to the biology or to human behaviour?

Another ethical issue is raised by recent work which suggests that sperm cells, and probably oocytes, could be obtained from *iPS* cells derived from skin cells. The only way of finding out whether they really are gametes (a spermatozoon or an oocyte) would be to discover when the cells are capable of fertilisation, i.e. participating in the creation of an *in vitro* embryo. Could such experiments be seriously considered and therefore the possibility of creating, in this context, an embryo for the purpose of research?

An additional problem arises in connection with the fact that scientists working in this field are pointing out the value of a possible medical application of this research if the approach were to give infertile individuals the possibility of producing gametes. Can we consider using ART to conceive and bring to term a child born of the skin cells of an adult?

Furthermore, a problem arises, similar to the one raised by *reproductive cloning*, that is the possibility of conceiving an embryo or even bringing a child to term, using sperm and oocytes derived from the skin cells of a single person⁷⁶.

In 1994, at a time when embryonic stem cell lines had been isolated for over ten years, using mouse embryos and other animal species, but not humans as yet, legislators did not consider there was any need to anticipate this possibility, although it was a very probable development. They banned any kind of research based on embryonic cells.

When (only four years later) human embryonic stem cells were isolated and possible medical applications were formulated, legislators decided to include these advances in their considerations and the law was modified: prohibition was replaced by prohibition with the possibility of derogation...

Rather than assuming that every five years, ethical reflection must be reinitiated *de novo* to take account of the status of scientific progress, **society would probably do better taking the route of prospective reflection, before instead of after the event, which would have the advantage of providing more time for thought and allowing debate to take place in a more serene climate.** It would also reduce the thunderbolt effect which leads either to a form of panic or to excessive and inappropriately enthusiastic acclaim.

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This possibility has been mentioned before, in particular in a “biology-fiction” book by Claude Sureau over ten years ago, entitled “*Alice au pays des clones*”. Stock. 1999.

A distinctive feature of such an embryo would be that it would be much closer, genetically speaking in particular, to its adult “parent” (male or female) than would be, in almost every case, an embryo created by “cloning” or nuclear transfer.

Ethical implications of respect for the beginning of life.

We have all been present to others before being aware that we existed. And we will all one day be absent to others without knowing that we no longer exist. Today's ethical and biomedical reflection, and the public debate it gives rise to, tend to focus on the two extremes of human existence: the beginning and the end of life. These are extreme times of transition, of passing and of thresholds. Indefinable thresholds where a human personality emerges or falters. Life which begins before the being emerges and sometimes persists after life itself. What will, perhaps, one day be, and will one day be no longer. Presence to oneself and future absence. Even though there is probably no true symmetry between emergence, the promise of a future being and the being's extinction; the end of a person who is no longer present, but who once was.

This insistence on two extremes, on conception and death, is constitutive of our respect for others. But it can also lead to the attenuation, or even the obliteration of respect. Because it is between those two extremes that the life of a human being unfolds. And respect, affection, tenderness in the beginning and at the end are only truly meaningful through the respect, the affection and the tenderness of which they are made — the stuff of our lives, the progression of our days. From birth to childhood, from childhood to adolescence, from adolescence to adulthood, from adulthood to old age, as long as persists within us the pulsation of awareness whose interruption defines — or so we have decided — the end, the end of the human being.

The essential ethical issues which are of concern to today's world are not those which bear on the earliest stages of development of future human beings, but rather on premature death and the sufferings of children and adults, caused by famine, infectious diseases, massacres, inhumane treatment, and the denial of health, liberty and dignity.

Concern for the earliest stages of the development of a future embryo should make us even more attentive and sensitive to the sufferings of children already born. Mentally handicapped children, who are so frequently deprived in this country of access to education and adequate assistance in places where they can be close to their families. The two million children in our country who live below the poverty threshold. The nearly ten million children under five years of age who die every year of disease and hunger in the world while the World Health Organization tells us that, collectively, we could have saved six million of them each year over the past several years. The 200 million children under five whose mental development will be hindered and interrupted by poverty, undernourishment and disease in the poverty-stricken countries of this planet.

CCNE considers that our respect for the earliest beginnings of human life must bear testimony to our fullest and collective commitment to respect for each person, child or adult, together with the will to prevent and repair to the best of our ability the tragic lives to which so many children are exposed from birth.

Ethical reflection on the earliest beginning of life becomes fully meaningful in this context alone.

Paris, October 21, 2010

Reservations expressed by certain members

Although we are aware of the distinctions made by this Opinion and the refinement of the reflection to which it leads, we must emphasise that the ethics of respect, referred to several times in the document, entails the exclusion of any form of instrumentalisation of human embryos.

The impossibility of defining an indisputable line of departure for when a person begins should not be confused with an absence of ethical and legal boundaries to our attitudes regarding human embryos. The enigmatic character of the embryo calls for respect. And this respect for embryos has primacy over practical consequences regarding their use.

In response to the point made regarding parental projects, we consider that the dignity of embryos does not stem from the plans other persons have made for them, but from the embryo's actual being, that is the development of a human life as such. As a consequence, while the boundaries presently set by law can be the subject of discussion, other common expressions of moral interdiction must be formulated. This interdiction bears on the rejection of any form of instrumentalisation of human life, even for research purposes. The inference is that respect has primacy and that only exceptionally can it be departed from.

As a result, as the Opinion does state, although it is not research as such which is a difficulty and although the fact that the destruction of spare embryos is provided for by law may appear to be ethically the lesser evil, it is the connection between the two which raises an issue. Using spare embryos for research opens the door to a justification of their production. We would wish that early attention be given to the possibility of reducing, or even ceasing, the production of cryopreserved embryos.

Furthermore, the creation of embryos for research purposes is unacceptable in our view since it is the most advanced form of instrumentalisation of an emerging human being.

In addition, a legal boundary would encourage scientists to continue research on other subjects of investigation besides human embryos. It also sets a curb on the logic of profit and competition.

François Beaufils
Marie-Thérèse Hermange
Xavier Lacroix
Chantal Lebatard
Claire Legras
Claude Matuchansky
Philippe Rouvillois
Michel Roux
Louis Schweitzer
Jean-Louis Vildé
Philippe Waquet