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Comitato Nazionale
per la Bioetica

Destino degli embrioni derivanti da procreazione medicalmente assistita e non più impiantabili

(26 ottobre 2007)

Presidenza del Consiglio dei Ministri
DIPARTIMENTO PER L'INFORMAZIONE E L'EDITORIA

THE DESTINY OF EMBRYOS RESULTING FROM MEDICALLY ASSISTED PROCREATION (MAP) AND NOT COMPLYING WITH THE CONDITIONS FOR IMPLANTATION

26th October 2007

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Presidenza del Consiglio dei Ministri

NATIONAL BIOETHICS COMMITTEE

NATIONAL BIOETHICS COMMITTEE'S OPINION ON THE DESTINY OF EMBRYOS RESULTING FROM MEDICALLY ASSISTED PROCREATION (MAP) AND NOT COMPLYING WITH THE CONDITIONS FOR IMPLANTATION

26th of October 2007

INTRODUCTION

The National Bioethics Committee (NBC) examined the "destiny" of embryos created for procreative purposes by extracorporeal techniques of Medically Assisted Procreation (MAP), which, after a morphological analysis, present such serious irreversible anomalies, that their implantation is not considered suitable and which, therefore, are not destined to achieve birth. This particular situation is anticipated by the guidelines presented in art. 3 of Law 40/2004 stating that, in the event that observational investigation should "show serious irreversible anomalies in the embryo's development", such embryos will not be cryopreserved, but left in culture until their extinction. Now, the presence of embryos in the abovementioned conditions constitutes a bioethical and legal problem of considerable importance. We must consider, on the one hand, that the research carried out on embryonic cells could be quite relevant for knowledge and therapeutic purposes and, on the other hand, that collecting pluripotent stem cells implies the need for an embryo that is still vital, but that current research generally leads to the suppression of the embryo.

The problem of the destiny of these residual embryos unsuitable for implantation, was examined by the NBC when drawing up the documents regarding *Bioethical considerations concerning the so-called "ootide"* (15.7.2005) and *Adoption for the birth (AFB) of cryopreserved and residual embryos obtained by Medically Assisted Procreation (M.A.P.)* (18.11.2005).

This topic has been examined by the previous NBC since 2005 through a working group coordinated by Prof. Luisella Battaglia and in which there were consistent contributions to the topic by Prof. Salvatore Amato, Prof. Adriano Bomipiani, Prof. Cinzia Caporale, Prof. Isabella Coghi, Prof. Francesco D'Agostino, Prof. Lorenzo d'Avack, Prof. Luigi De Carli, Prof. Maria Luisa Di Pietro, Prof. Luciano Eusebi, Prof. Angelo Fiori, Prof. Carlo Flamigni, Prof. Aldo Isidori, Prof. Demetrio Neri, Prof. Laura Palazzani, Prof. Alberto Piazza, Prof. Giancarlo Umani Ronchi. During those working sessions a lengthy debate on the possible bioethical and legal solutions took place, along with the acquisition of scientific documents and written observations. Because the previous NBC's mandate had expired, it was not possible to draw up a text summarising

the main points, which could be brought to the Committee's attention in a plenary meeting.

Therefore, once the NBC was reappointed, the Committee felt it necessary to reconsider the issue, establishing a new working group coordinated by Prof. Lorenzo d'Avack and including Prof. Salvatore Amato, Prof. Adriano Bompiani, Prof. Stefano Canestrari, Prof. Elena Cattaneo, Prof. Isabella Coghi, Prof. Roberto Colombo, Prof. Francesco D'Agostino, Prof. Antonio Da Re, Prof. Carlo Flamigni, Prof. Marianna Gensabella, Prof. Luca Marini, Prof. Assunta Morresi, Prof. Demetrio Neri, Prof. Laura Palazzani, Prof. Alberto Piazza, Prof. Monica Toraldo di Francia, Prof. Giancarlo Umani Ronchi, Prof. Grazia Zuffa, Doctor Riccardo Di Segni.

The document, presented in the plenary meeting of the 20th of October 2007, has been largely discussed and subjected to further revision, especially with regards to the observations about one of the bioethical positions voiced by Prof. Adriano Bompiani, Prof. Roberto Colombo, Prof. Bruno Dallapiccola, Prof. Antonio Da Re, Prof. Maria Luisa Di Pietro, Prof. Marianna Gensabella, Prof. Luca Marini, Prof. Assunta Morresi, Prof. Andrea Nicolussi, Prof. Vittorio Possenti, Prof. Rodolfo Proietti, Prof. Lucetta Scaraffia, Prof. Giancarlo Umani Ronchi. During the plenary meeting of the 26th of October 2007, the document has been agreed upon by those present with the abstention of Prof. Elena Cattaneo, Prof. Cinzia Caporale and Prof. Grazia Zuffa. Prof. Laura Palazzani, who could not participate in the meeting for justifiable reasons, gave us her early agreement to the document.

The importance and the innovation of the document can be found in particular in the fact that within this problem NBC members discussed and examined the possibility of identifying an assessment criteria for the embryo's death, when the embryo is still partially vital, so that embryonic cell donation to research is possible, establishing an analogy with organ donation *ex mortuo*. This hypothesis seemed interesting from a bioethical point of view.

Some members considered this analogy as tenable and hoped that the scientific world would accept the embryo's death when certain physical conditions prevent the embryo from developing (organismic death). And if the removal and use of living blastomeres from an embryo who has been declared dead can be compared to the removal of organs and tissues from an individual who has been declared dead, then the donation of blastomeres to research is ethically licit. Other NBC members did not agree with this hypothesis because they did not consider as valid the analogy between ascertaining the "total cerebral death" of someone who has already been born, for the eventual purpose of removing the organs, and ascertaining the embryo's "death due to interruption and degeneration of development", for the eventual purpose of removing one or more still vital blastomeres. In order to better explain the reasons for such disagreement, some NBC colleagues chose to draft a personal remark. Prof. Zuffa also gave the reasons of her abstention in personal remark. Both these documents, as is tradition when drawing up NBC's opinions, have been attached to the text and published in its context.

In conclusion, the document presented here comes from a discussion that covered the variety of positions existing on this issue and clarified the more complex and controversial problems, identifying the solutions and the reasons for them.

The President

Prof. Francesco Paolo Casavola

DOCUMENT

As known, the Italian Bioethics Committee, like other National Committees, pays constant attention to bioethical problems regarding the human embryo, which is already the object of previous documents by the Committee.

1. The problem under examination

The NBC's document simply considers the "destiny" of embryos created for procreative purposes by extracorporeal techniques of MAP, which, after a morphological analysis, present such serious irreversible anomalies, that their implantation is not considered suitable and which, therefore, are not destined to be born, also after the contextual refusal of the mother who, adequately informed, refuses to proceed with the procreative project.

This situation of the embryo is anticipated by the guidelines presented in art. 3 of Law 40/2004 stating that, in the event that observational investigation should "show serious irreversible anomalies in embryo development", such embryos will not be cryopreserved, but left in culture until their extinction.

It must also be considered that the way in which the extracorporeal techniques of MAP have been applied in Italy, until the Law 40/2004 came into effect, has led to the existence of a considerable number of cryopreserved embryos, which could still be brought to birth. Even the Law 40/2004, although it generally forbids cryopreservation, in article 14, subsection 3, states that in the case of serious and documented unforeseen circumstances with regards to the woman's health conditions, the cryopreservation of the embryos is allowed "until the date of transferral, to be carried out as soon as possible". This possibility is then extended to the guidelines, on the application of article 14, which allows cryopreservation "in case a transferral has not taken place". This extension of the normative text has led to the hypotheses of embryo's missed transferrals to go beyond the simple cause of unforeseen circumstances with regards to the woman's health or her mere refusal, so that the embryo's transferral is non-coercible and can be postponed to another time[1].

The abovementioned circumstances therefore take into account the possibility that the mother could at a later stage ask for the procreative course to resume through the embryo's defrosting and implantation. We must keep in mind that, according to scientifically proven data, 30-35% of embryos after being defrosted die or are not biologically suitable for implantation in the uterus.

These events can, therefore, increase even further the number of embryos presenting serious anomalies and not suitable for implantation.

Finally, law 40/2004 forbids research and any form of non-therapeutic experimentation on embryos (art.13). However there is no normative provision regarding research on embryonic stem cells that have not been produced in Italy.

The current existence of embryos in the abovementioned conditions constitutes a considerable bioethical and legal problem. We must consider, on one hand, that the research carried out through embryonic cells could be very important for knowledge

[1] Guidelines. Limitations on the applications of the techniques on embryos.

and therapeutic purposes and, on the other hand, that collecting pluripotent stem cells implies the need for an embryo that is still vital, but that current research generally leads to the suppression of the embryo. This problem, already discussed by the NBC in the recent documents concerning the ootide[2] and the adoption for the birth of cryopreserved embryos (AFB)[3], has been taken into account by a previous working group. Because the previous NBC's mandate expired, it was not possible to draw up a text summarising the main points, which could be brought to the Committee's attention in a plenary meeting. However during those working sessions a lengthy debate on the possible bioethical and legal solutions took place, with the acquisition of scientific documents and written observations, all of which has been taken into account when drawing up the present opinion.

2. Comparison of opinions

Within the NBC a variety of bioethical positions have emerged, all of which are presented as follows.

a)= A bioethical possibility is the one that, although not denying protection and respect for the human embryo, believes that the embryo's destination to research can be justified, with the informed consent of the biological parents when they are not in a "state of abandonment", even if this results in a destructive outcome for the embryo. Those who support this solution assume that, before their extinction, it is legitimate to donate their cells for solidarity purposes. In addition, unlike other procedures (experimentation on embryos still suitable for implantation, pre-implantation diagnosis, etc.), in this case it is not about considering the embryo's birth as a subordinate, subsequent hypothesis, one not to be considered as the embryo's objective, because this event will not ever take place; rather then turning the embryo's natural death into a donation, avoiding any exploitation and considering the embryo as a good in him/herself.

Within this line of thought two different positions have emerged, which we summarised here.

Even believing that in the most complex bioethical cases the embryo must be treated as a proper human life (even in the case of uncertain judgement about the embryo's ontological state), some members state however that in the case of formed or defrosted embryos, who are destined to die in any case because they are non-transferable due to the presence of serious and irreversible anomalies, the embryo's protection finds its limit. This is because such protection has meaning only if the highest possible bioethical value is at play, that is: life, which is not the case in the circumstances we are referring to, as the embryos that are unsuitable for implantation are not in any case destined to culminate their existence with the achievement of birth.

Others, even agreeing with this proposition, find it limiting because it restricts the legitimacy of scientific research only to embryos that present "serious irreversible anomalies in development". These members, starting from different evaluations regarding the embryo's ontological state, believe that embryos' donations to research should also include the cryopreserved, residual embryos, those in a state of abandonment and for which a parental project is no longer possible. The reasons for this position have already been expressed in the *NBC's opinion on the therapeutic use of stem cells* (2000), paragraphs 21, 22 and 31.

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[2] Bioethical considerations concerning the so-called "ootide" (15.7.2005).

[3] *Adoption for the birth of cryopreserved and residual embryos obtained by medically assisted procreation)* (18th November 2005).

b)= The other position believes that any exploitative use of the embryos with destructive outcome is never ethically acceptable because it is contrary to their intrinsic dignity and to their right to life. The members who support this position underline that the scientific evidence of contemporary embryology – already reported in the NBC's document *Bioethical considerations concerning the so-called "ootide"* – shows how the spermatozoon's fusion/activation or microinjection/activation in the cytoplasm of the egg cell is the primary event, irreversible and fundamental, which starts the process of creation and development of the human embryo, towards which any intervention, of any kind, that is not aimed at the embryo's good, is not ethically acceptable. Therefore, the embryos that are not transferred to the uterus because of serious irreversible anomalies in development should be left in culture until their "natural death". This position, like the one reported in section a), has also been explained in the *NBC's opinion on the therapeutic use of stem cells* (2000) and it has been agreed upon by the majority of the NBC in the following document *Opinion on research utilising embryos and stem cells* (2003) in which we read: "experimentation on embryos is justified only if practiced in their specific interest and cannot be justified by the (still relevant) general interest of society and science and therefore it cannot result in their destruction".

3. The search for a common position with regards to the definition of "embryo's death".

Within this problem, NBC's members have discussed and examined another possibility: the possibility to identify a criterion to ascertain the "embryo's death", which would make it possible to donate embryonic cells to research, establishing an analogy with organ donation *ex-mortuo.*

This hypothesis seems interesting from a bioethical point of view and has been the object of particular attention, using also materials and evaluations acquired in previous NBC's documents.

During a wide and in-depth discussion it has been highlighted that prevailing ethical points of view, like in many countries' legislature, consider organ donation *ex-mortuo* – when it is not in conflict with the idea of sacredness and intangibility attributed to human remains – as an "act of human love". But it is also known that civil society, to make this act real and licit, has had to face the problem of *ascertaining the donor's death*. As dying is a process rather than an event, it cannot be directly identified by an empiric diagnosis or method. However, within the precautionary principle, the so-called *criteria to ascertain death*, intended as the definitive and irreversible conclusion of the dying process, have not been rejected. From this perspective, the total and irreversible cessation of every encephalic activity (cerebral encephalic death), if scrupulously applied, has an adequate scientific foundation.

a)= Some NBC members hypothesize that in a similar way the embryo's death could be ascertained by certain physical conditions which would hinder the embryo's development (organismic[4] death, according to an expression not yet consolidated in

[4] Terminology used in the document by L. DE CARLI, *Notes for the working group on:* "Cell donors supernumerary embryos" and in the document Alternative Sources of Human Pluripotent Stem Cells (May 2005), issued by the U.S.A.'s The President's council on Bioethics. Also look at: D.W. LANDRY-H.A. ZUCKER, Embryonic death and the creation of human embryonic stem cells in "Journal of Clinical Investigation" (2004), vol. 114:1184-6; C. HOLDEN, Stem cells. Scientists create human stem cell line from "dead" embryos, in "Science", 2006, Sep. 29; 313 (5797), 1869; R.M.

the scientific world). Although some of his/her cells are still vital, the embryo as biological individual would die if he/she clearly lost the capability to continue his/her development in an integral, self-regulated manner and through a progressive cellular differentiation. Some parts of the embryo would still be vital (one or more blastomeres), but the whole would have lost his/her vitality, in analogy with what happens in the process of cerebral death, where some of the corpse's organs remain vital (the heart, the kidneys, etc.), although it is possible to consider the individual as being clearly destroyed (that is, dead). And if the removal and the use of live blastomeres from an embryo who has been declared dead can be compared to the removal of organs and tissues from an individual who has been declared dead, then we can deem as ethically licit the donation of blastomeres to research. This perspective, like in the case of the donation *ex mortuo*, recalls the *charity principle* that, although with different emphasis, is a common trait of the most important moral doctrines, inspires the ethics of biomedical research and is the source of the duty of responsibility that we have towards people who suffer and society on the whole.

NBC members who agree with this series of considerations and share the thesis that the analogy between the donation of organs *ex mortuo* and the donation of embryonic cells is ethically licit, hope to identify secure scientific parameters to declare the embryo unable of further development, so that the donation of his/her cells to research is made possible, without ethical objections being raised. Finally, they believe that the autonomy and responsibility of the scientific world has the task to identify the assessment criteria for the embryo's irreversible inability to develop, as was the case for human death.

b)= Other NBC members do not agree with this hypothesis because they do not consider as valid the analogy between ascertaining the "total cerebral death" of someone who has already been born, for the eventual purpose of removing organs, and ascertaining the embryo's "death due to interruption and degeneration of development", for the eventual purpose of removing one or more still vital blastomeres. In fact, in the second case, it would not be about ascertaining an organ's (the brain's) loss of physiological functionality, which compromises the coordination and the integration of the whole organism, but about evaluating an embryo's inability to develop regularly, which depends on complex molecular and cellular interactions, ensured by a series of activations/deactivations of the genome. The observation of morphological phenomena allows us to evaluate the development of the embryonic organism before implantation from the point of view of the relationships between the "parts" (cells) and the "whole" (zygote, pre-morula, morula, blastulae), but it does not allow us to immediately create a functional analogy with the foetus or the infant or the adult in the identification of a centre organizing the "whole" (or "critical centre") which, should it cease, would lead to the cessation of the integration and coordination of the embryonic organism in an early phase of development (the so-called "organismic death").

To ascertain the embryo's death according to criteria that differ from observing apoptosis in all blastomeres (which would impede the use of the embryo's cells), we would have to use, in any case, "probability" signs and not certainties, which would make it difficult to decide to use the embryo for aims different from the implantation for procreative purposes. This perspective would legitimise the use of embryos declared non-transferable, in conflict with the embryo's high level of

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GREEN, Can we develop ethically universal embryonic stem-cell lines?, in "Nat. Rev. Genet.", 2007, 8 (6): 480-5.

protection, as also stated in Law 40/2004. What this perspective has stated does not mean excluding or minimising the value of the attempts to give an answer to the question of the definition and the assessment criteria of the death of the embryo in vitro, but it means – on the contrary – underlining the need to acquire in depth and wide knowledge through the study of adequate experimental models in animals and with the contribution of other disciplines like philosophy and jurisprudence. Instead, in effect the current analogy could turn into a regressive instrument eroding the concept of man, which is already fully institutionalised in our Constitution, founded on the guarantee, without discriminations, of man's fundamental rights and on promoting the full development of the individual.

4. Conclusions

Offering the aforementioned considerations to the attention of public opinion, the Committee hopes that the scientific community will study in depth the problem of identifying the assessment criteria for the "embryo's organismic death" considered in the early stages of the in vitro development; a problem that has emerged within the NBC as an "hypothesis of work" of bioethical interest.

NBC's documents of reference

NATIONAL BIOETHIC'S COMMITTEE, *Identity and status of the human embryo,* 1996; ID., *NBC's opinion on the therapeutic use of stem cells,* 2000; ID., *Opinion on research using embryos and stem cells,* 2003; ID., *Adoption for the birth of cryopreserved and residual embryos obtained by medical assisted procreation (MAP),* 2005; ID., *Bioethical remarks on the so-called "Ootide",* 2005.

PERSONAL REMARKS

Personal remark signed by Prof. Adriano Bompiani; Prof. Roberto Colombo; Prof. Francesco D'Agostino; Prof. Bruno Dallapiccola; Prof. Maria Luisa Di Pietro; Prof. Marianna Gensabella; Prof. Aldo Isidori; Prof. Assunta Morresi; Prof. Andrea Nicolussi; Prof. Laura Palazzani; Prof. Vittorio Possenti; Prof. Rodolfo Proietti; Prof. Lucia Scaraffia.

The signatories of this personal remark, although agreeing – as the other NBC members – with the position expressed in paragraphs 2b and 3b of this *Document*, want to clarify and add their scientific and ethical argument as follows:

1. In the *Document* the concept of an embryo's "unsuitability to implantation" comes from both reasons that are *intrinsic* to the embryo's state (that is, the "recognised non-compliance with the conditions for implantation" or the "inappropriateness of implantation" according to a biological-clinical judgement elaborated on the basis of microscopic observations of anomalies in the *in vitro* development; cf. *Guidelines* of the Law 40/2004, art. 13), and also from reasons that are *extrinsic* (that is, the "non-carrying out the implantation" due to unforeseen circumstances in the woman's health conditions; cf. Law 40/2004, art. 14, subsection 3), and also, finally, from the shared need, both ethical and legal, "to consider as non-coercible, the embryos' transferral" into the mother's body, in any circumstance (Document, paragraph 1; cf. *Guidelines* of the Law 40/2004, art. 14). The signatories of this personal remark believe that we can rigorously talk about "unsuitability to implantation" only when referring to embryos that are characterised by serious and irreversible anomalies in their development and that this concept cannot properly include the "non-transferred" or "abandoned" embryos, which, although have not been "implanted", are however in theory and in practice "implantable" (for these embryos' treatment the *Guidelines* of the Law 40/2004 advise their collection in a National Cryopreservation Centre and the NBC, in 2005, in one of its *Opinions* gave value to the ethical principle of the so-called "adoption for the birth").
2. Incidentally, we must stress that the reference to "[the embryos'] such serious irreversible anomalies, that their implantation is not considered suitable" (*Document*, paragraph 1) demands, for a comprehensive ethical evaluation of the problem discussed in the *Document*, the consideration that such anomalies do not occur only because of natural causes (that is, those that can also occur in the non-medically assisted *in vivo* fecundation), but are also and considerably due to biotechnical causes, that are well documented in scientific literature, as they are due to the laboratory procedures of the *in vitro* fecundation (in particular, the gametes' micromanipulation, which is required by the common technique of the intracytoplasmic injection of the spermatozoon [ICIS] and of the embryos in culture before their transferral *in the uterus.*
3. Ascertaining that a human embryo's "unsuitability to implantation", as a scientific judgement that comes from evident signs of irreparable pathology often caused by the techniques themselves, does not coincide

with ascertaining the embryo's "death": due to the fact that scientifically rigorous criteria to compare the "unsuitability to implantation" to "death" do not exist, the experimentation and destruction of embryos deemed "unsuitable for implantation" is not ethically justifiable, just like the diagnosis of an incurable disease or the imminence of death does not justify non-therapeutic clinical trials on the patient. Currently, we cannot realistically foresee any research on embryos "unsuitable for implantation", that can also have a therapeutic value for them – that is, that would allow them to start developing normally again and therefore to become "suitable for implantation" – therefore it is not ethically licit "to donate" these embryos for experimentation which would allow progress in biological knowledge that is basic or applied to cellular therapy, through their manipulation and destruction. The embryos that are "unsuitable for implantation", even if characterised by serious anomalies, are human beings at the initial state of their development, and have, therefore, absolute dignity, which forces us to always respect and protect their lives.

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Personal remark signed by Prof. Grazia Zuffa.

The reasons for my abstention with regards to the document titled "National Bioethics Committee's opinion on the destiny of embryos resulting from MAP and not complying with the conditions for implantation" do not reside in reservations regarding the operative indications: in fact I agree with the position (expressed in the document) of those who believe that it is ethically licit to donate to research the embryos that will not be able to develop in any case, nor be transferred in the uterus due to serious and irreversible anomalies.

However, I do not agree with the philosophical arguments underlining the choice and in particular the line that seems to lead towards a shared position: the search for an assessment criterion to ascertain the "embryo's death", which would "make it possible to donate embryonic cells, establishing an analogy with organ donation *ex-mortuo"* (paragraph 3).

It is this analogy that provokes the biggest perplexities: the use of meaningful words like "death" and the proposed assimilation between the "unborn" embryo and the "already born" human being, risks "putting within brackets" and overshadowing the event of the birth as "coming into the world".

That is, we talk about the embryo's "life" (and death), in effect reducing to insignificance the indispensable mediation of the woman's body and mind to put a living creature into the world. All this leads to a symbolic sliding towards a purely biological dimension for fundamental human events, like birth. I fear that the "ethical hook" searched for by many to give "meaning" to biological material separated from living bodies, is not part of the scientific answers regarding the parameters of the embryo's "organismic death". On the contrary, it is this reasoning, as if the "life being born" could do without the woman's mediation, that shows (and promotes) the symbolic confusion brought by the use of technologies in procreation.

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