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Anthropological and ethical reflections on the production and use of embryonic stem cells

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Abstract. Stem cells and their potential therapeutic application have generated tremendous public interest, great enthusiasm among researchers and intense commercial interest. There are diverse sources of stem cells. According to their origin and their biological characteristics, they are classified as embryonic stem cells, germline stem cells and tissue stem cells. Until now, the most concrete therapeutic results have come from some adult tissue stem cells, with promising prospects also being offered by umbilical cord stem cells. Regarding embryonic stem cells, there is concern that they would be difficult to control *in vivo*. Nonetheless, many researchers are still pursuing their potential uses, convinced that they will be useful not only for study, but also for therapy, especially as a result of their high capacity for self-renewal as well as their broad potential for differentiation. This discussion which is eminently scientific in nature, and not lacking in ethical and political repercussions, will not be entered into above all regarding the allocation of available intellectual and economic resources.

EMBRYOS AS A SOURCE OF BIOLOGICAL MATERIAL

At present, the main source for human embryonic stem cells is the inner cell mass of human blastocysts. At the heart of the ethical and legal questions concerning the production of these, the question of the value is attributed to the life of an early human embryo and the respect which, by right, it should be accorded.

In the debate over identity and value of the early embryo, there are diverse positions with very different ethical outcomes. At the Pontifical Academy for Life, our position is situated among those that recognize the value of embryonic life and hold that in regard to an embryo's existence, and it is necessary to proceed with the same respect that is ordinarily owed to all human life. The position has been broadly illustrated and argued by philosophers, theologians and jurists. This does not mean obviously, that even in this perspective, the comprehension of ontological status of the embryo is still without some grey areas, because it is not immediately

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This article seeks to focus on the principle ethical problems connected with the use of human embryos as the source for stem cells and offers some reflections on alternative means to obtain embryonic type stem cells without having to destroy embryos or having to go through the process of creating them.

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possible to apply to embryonic life categories that have been originally elaborated in reference to adult life. Notions such as of 'organismic life', of 'rational nature' or of 'human being' have been developed in a very different anthropological context with respect to these first stages of human life. We assume the general assertion that innocent human life deserves respect from its onset to its decline, from the time of conception until death, and, therefore, the intentional and direct destruction of a living human embryo at whatever stage of development, and for whatever reason it may be done, is unacceptable.

This assertion about value of the life of the embryo does not depend on the manner nor the circumstances in which this life begins. The fact that an embryo is derived from the fusion of gametes *in vivo* or *in vitro*, or is generated in an agamic way, as in the case of cloning, does not change its moral status because the concrete modality by which a new human being is called to life does not change the ontological and ethical quality of his or her existence. A clone belongs to the human species; it develops according to the human mode of development and, from what we already know from animal cloning, given adequate conditions can give rise to and bring to term a new individual of its own.

The relationship between the production of stem cells and cloning arises due to the prospect of being able to create stem cells that are immunologically compatible for a recipient thus bypassing the problem of rejection. In effect, the universal opposition to human cloning, already sanctioned in public documents of notable prominence and authority (e.g. UNESCO, *Declaration on the Human Genome & Human Rights* 1997, European Parliament, *Resolution on Human Cloning* 2000) demonstrates signs of a shift towards approval when it concerns the issue of cloning for scientific and therapeutic ends. In the UK, for example, where the production of embryos is already allowed for research, the *Report of the Donaldson Commission* in 2000 opened the way for therapeutic cloning of human beings (Chief Medical Officier's Expert Group 2000). A clear distinction was introduced between therapeutic or research cloning and reproductive cloning and it was proposed to reserve the term 'cloning' to describe reproductive cloning in order to avoid the moral difficulties connected with human cloning (Solter & Gearhart 1999). Therapeutic cloning is thus referred to as 'cell nuclear replacement' or 'cell nuclear transfer'. Obviously, from an ethical point of view, the end pursued in giving life to a human being, whether it be for a procreative or practical end, does not change the negative judgement concerning the application of cloning techniques to human beings.

We wish, moreover, to emphasize that therapeutic cloning drastically alters the human meaning of 'generation' so as to render it no longer thought of or performed for reproductive ends, but rather programmed for medical-experimental and even economic purposes. This negation of the meaning of human generation is radical: whereby, through generation, no matter how it happens, a human life is brought into existence, in therapeutic cloning and in every form of procreation pursued for similar instrumental ends, one destroys a life after giving it an ephemeral existence. As affirmed, 'Generation by cloning, of a human individual for the purpose of using it as a source of stem cells ... is an action unworthy of the human person because it is opposed to his good and no good intention or particular circumstance is capable of removing the evil' (Pontifical Academy for Life 2001). Not only is it illicit to actively suppress an embryo to remove biological material, it is also ethically unacceptable to even harm the integrity of the embryo so as to arrest irreversibly its development or inflict damage that leads to death.

In addition, worthy of mention is the technique of obtaining embryo stem cells from single blastomeres taken from embryos in a stage of development prior to becoming blastocysts (Klimanskaya *et al*. 2006). The protocol is similar to that used for pre-implantation diagnosis, and although it does not necessarily involve the suppression of the embryo, it is certainly not without risks to its initial development and its subsequent implantation. Until now, it does not

seem that it has been possible to obtain blastomeres without losing the embryo; still, there are two additional objections: when a still totipotent blastomere is taken from the embryonic organism, a kind of cloning *via* embryo splitting is obtained; second, we are in front of an intervention that does not directly foresee the good of the embryo whose existence is placed at risk, in the very first days of its development, for an end that is extrinsic to it. We remember that one must also value in this context the general principle that any medical intervention to the embryo, whether diagnostic, therapeutic or for the ends of research, must always have as its primary end the attainment of a *significant* benefit for the embryo itself, namely a benefit that is proportionate to the possible risks to which it is exposed.

RECOURSE TO SPARE EMBRYOS

There exists wide international agreement – apart from certain significant exceptions, such as the UK – concerning the illicity of creating a human embryo for the exclusive ends of research. However, in many countries, there is ongoing ethical and legal debate on the experimental and therapeutic use of embryos derived from the techniques of *in vitro* fertilization and which remains unused, above all those embryos in the state of cryopreservation. As understandable in some quarters (often those who favour experimental use of spare embryos pre-suppose that the life of the early embryo, or so-called pre-embryo, does not have value in itself, or, at the very least, has less value than the life of human beings who are born) consequently, the degree of protection owed to the embryo can be balanced with, the at least equivalent concern, for cure of the sick. We must also note that among those who, in general, support the norm of respect for life of the embryo, there are some open to the possibility of the use of 'spare' and cryopreserved embryos. They hold that these are condemned to extinction anyhow and therefore to use them for ends that may be useful for persons neither changes nor worsens their destiny, while at the same time procures benefits for others. It is our view that the destiny of death that these spare embryos face does not remove the gravity of their intended elimination, but rather ought to bring us to prevent – as in fact is anticipated in some legislations – their very creation. We cannot produce embryos *in vitro* beyond the reasonable possibilities of transfer and then, because they are defective or spare, send them to destruction.

If we take seriously the affirmation of the true humanity of the human embryo at whatever stage of development, we cannot apply to the embryo a utilitarian or instrumental logic that we could not apply to a child. No one, I believe, would say that we can take the organs from a sick child in a terminal state, because taking them simply anticipates an inevitable death, and using them to cure another child. The life of a human being can never be exploited and become a means for the attainment of good ends; the good end cannot justify the evil means. To not use these embryos may seem a waste of extremely useful biological material, but to permit their use introduces an exception with grave and serious consequences for the norm of respecting, always and in all cases, innocent life. Pope John Paul II (1995), in the encyclical letter *Evangelium Vitae*, saw in the use of embryos for research an unacceptable objectification of human life that reduces it, 'to simple "biological matter" to be freely disposed of'. Some think that the state could dispose of these embryos that are orphaned or in a state of abandonment, while others place as the condition for the licit use of such embryos the consent of their biological parents. But neither the state nor the biological parents have this right over unborn life. These same parents are not the owners of the embryo, but rather the guardians and caretakers of the human life that has been entrusted to them.

It has been proposed to give to research only those embryos in which, after unfreezing death as an organism, have been ascertained. From the theoretical point of view, this hypothesis is worthy of consideration, but from the practical point of view it raises some questions that must still be examined closely. The first is pinpointing objective criteria for the verification of embryonic death, for there is a need to be attentive in distinguishing between the state of non-vitality, non-implantibility and impossibility of complete development. The signs of embryonic death must establish the irreversible loss of functional unity of the embryo, namely the loss of its self-organization. The second is to decide what to do with embryos that, once unfrozen, reveal themselves to be still alive and implantable. According to some, they could be given for prenatal adoption, with all the problems associated with this. According to others, they could be left to die, considering that there does not exist a means to keep them alive and that the frozen state represents an extraordinary means and thus not a duty. In effect, all solutions proposed to the problem of cryopreserved embryos are perplexing because we are confronted with an absurd situation, namely that of cryopreserved embryos. The disordered situation itself within which ethical reason must enter to function in this case profoundly colours the attempts at a solution (Faggioni 1996).

USE OF EMBRYOS AND COOPERATION WITH EVIL

There exist many lines of embryonic stem cells that have already been established and are available for research, but for diverse reasons, bound as one says, to the very needs of experimentation, there is a demand for the establishment of further such lines. For proportioned reasons, recourse to existing lines is not to be considered in itself morally illicit, because it does not lead to the creation or destruction of more embryos; recourse to new lines of stem cells creates more serious ethical dilemmas. The situation becomes paradoxical when one is dealing with the use of stem cells produced legally in certain countries and imported to other countries where the production of spare embryos or the manipulation of embryos is prohibited. From the moment that it is known that their production has involved the destruction of embryos, one asks if the use of these stem cells does not constitute a form of illicit cooperation that is a form of participation in an evil project.

In order to make ethically clear the concrete situations that are not always straightforward, moral tradition has elaborated a rather sophisticated explanatory scheme to clarify the issues at stake. One speaks of formal cooperation when one shares in some way the intention of the one who carries out the evil act: this is obviously illicit because there is true and proper complicity. One speaks of material cooperation when one actually cooperates in an evil act, but without internal agreement: this can be immediate or later. If one directly cooperates in the execution of the evil act, this is illicit. In other cases, the cooperation is mediated or indirect when one takes part in creating the conditions in which it is possible to carry out the evil act. The principle is that the further away one is from the collaboration, the more the action is justifiable. From a limited perspective, a scientist could be at peace if he used imported embryonic stem cells, perhaps without having any relationship with the centre that produced them, but we cannot shy away from the fact that there exists a necessary connection precisely between the demand of the ESC and their production.

For these reasons, the Pontifical Academy for Life, in the *Declaration on the Production and the Scientific and Therapeutical Use of Human Embryo Stem Cells*, has reasserted that it is not licit for a researcher to use embryonic stem cells supplied by another researcher or that are

commercially available because, 'prescinding from the participation – formal or otherwise – in the morally illicit intention of the principal agent, the case in question entails a proximate material cooperation in the production and manipulation of human embryos on the part of those producing or supplying them' (Pontifical Academy for Life 2000).

NEW WAYS OF OBTAINING EMBRYONIC STEM CELLS

In the effort to overcome ethical and legal obstacles related to the destruction of human embryos, studies are being performed in search of obtaining cells with characteristics analogous to embryo stem cells without the need to manipulate or destroy embryos. It could simply be an attempt to take the heat off the debate, enabling easier access to funding, but – in our opinion – the sole fact of pursuing the objective to have stem cells without destroying embryos is a sign of moral sensibility on the part of the researchers and merits praise and careful consideration. The challenging question remains that of elaborating an ethical evaluation of the proposed individual procedures. An important and well-balanced contribution to this reflection has been offered by the White Paper of the US President's Council of Bioethics entitled 'Alternative Sources of Human Pluripotent Stem Cells' President's Council of Bioethics (2005).

Good intention and the end pursued by research cannot exempt us from evaluating honestly the proposed methods and concrete modalities with which the experiment is to be conducted. Here, the general principle is also valid, that a good intention does not make good or just a kind of behaviour that is intrinsically disordered. Some researchers have succeeded in obtaining *parthenotes* from the parthenogenesis of human ova, making them mature until the blastocyst stage and deriving stem cells from them (Brevini *et al*. 2006). The biological and ethical discussion on the nature of the parthenote is ongoing (Marchant 2006). Some believe that the parthenote, notwithstanding its agamic origin, is a true and proper embryo because it develops in an analogical mode to normal embryos and, in effect, produces blastocysts with a normal appearance. From the biological point of view, the parthenote must be recognized as an individual human organism, with typical characteristics which, normally, every other human being possesses at the same stage of development. Others maintain that the parthenote, not being an embryonic structure attributable with certainty to the human species, is rather to be considered a pseudo-embryo or an embryo-like structure: the fundamental reason being in the unnatural constitution of its genome that derives from the duplication of haploid ovocytic patrimony and that therefore does not present the characteristic genomic imprinting of the human species. An indirect proof to support this second interpretation would be the impossibility to develop itself correctly, even if the appearance of the parthenogenetic blastocysts is normal. The difficulty in obtaining human ovocytes, fresh or frozen, in large quantities constitutes a practical limit to widespread application of this method. It could be interesting for the researchers who do not want to use human embryos and for those countries in which there does not exist the possibility of access to spare embryos obtained from *in vitro* fertilization and from Intracytoplasmic Sperm Injection.

Other groups have hypothesized the transfer of genetically altered nuclei (*Altered Nuclear Transfer*) into denucleated oocytes, through the silencing of some genes. In the experiment of Meissner and Jaenisch, the function of gene *Cdx2*, indispensable for the formation of the trophoblast and the nidation of the blastocyst, was silenced (Meissner & Jaenisch 2006). The silencing was obtained through a technique of interference with short hairpin RNA and was reversible. Sustainers of this method affirm that silencing produces biological artefacts lacking the potential to develop into normal human embryos. This intervention does not manipulate an already formed

embryo, but preceeds any such true and proper formation of an embryo. The result of the operation is not an embryo, but a structure biologically inadequately organized, a nonembryo.

Others favour the idea of dealing with a defective or disabled cloned embryo and not a biological artefact. In our opinion, one is in front of a type of cloning in which the embryo is deliberately deprived of an essential characteristic for its complete development: its genome, derived from a diploid cell, is intact, even if its expression is altered. The proof of this is that the silencing is reversible. A variant of Altered Nuclear Transfer currently being studied, proposes the transfer of a somatic nucleus that has been induced to produce high quantities of the factor *nanog*. This factor would be absent in the first stages of development of the embryo composed of totipotent blastomeres and would appear only with the appearance of the pluripotency. Alternatively or concomitantly, mRNA for this same factor could be introduced into the oocyte prior to nuclear transfer (*oocyte assisted reprogramming*). As in the preceding case, here one asks if the biological entity so produced would be radically different from a human embryo, obtained by cloning with transfer of normal nuclei or with the transfer into non-reprogrammed oocytes. Without entering into details of experimental methods performed or hypothesized, the general rule is valid, that when there exists the scientifically based doubt as to whether one finds oneself in front of a living human embryo or not, even if in unnatural conditions or deprived of some functions, this reasonable doubt would already be sufficient to demand in all situations the unconditional respect that is morally due to the human being.

A different approach from above has been proposed by doctors Takahashi and Yamanaka, researchers at the University of Kyoto (Takahashi & Yamanaka 2006). They did not produce embryos or structures similar to embryos but attempted to rejuvenate epigenetically adult somatic cells, reprogramming the nuclei through retroviral transduction of four factors that are important for conserving the quality of stem cell: Oct3/4, Sox2, c-Myc and Klf4. If the experiment, conducted with success on mouse fibroblasts, was to be reproducible also in human cells, it would open up the possibility of making adult stem cells more similar to embryo stem cells, without the need to use embryos. This method, if technically feasible and capable of answering our expectations in terms of biological quality, could be used without ethical dilemmas. There is no doubt that it would be better if, one day, we would be able to 'reprogram' a somatic cell of an individual adult, in such a way so as to transform it into an adult stem cell or, even better, to reconvert it to its undifferentiated state and then, perhaps, to induce it to differentiate into a specific type of tissue diverse from that which the cell belonged before the 'reprogramming'. One could have stem cells without producing embryos and the problem of incompatibility would be overcome because the stem cell produced in this way would be autologous. In order to transform the hopes into reality, further studies and research are necessary with the patience to test it extensively on animals before passing to humans.

To finish, I would like to underline the fascinating possibility of turning back the clock of life through the process of reprogramming that is true and proper orientated dedifferentiation. Man has the possibility to intervene in the stream of development and, in a certain sense, in the running of the biological clock that we have always considered one directional in an evolutive sense.

FINAL CONSIDERATIONS

The entire discussion, concerning the use of embryonic stem cells, centres around the wider question of the relation between scientific reasoning on the one hand and ethical reasoning on the other, and questions the role and the goals of science in the middle of a complex society.

In many countries of the world, the general public receives an unsettling message that ethical and legal obstacles placed in front of the use of embryonic stem cells, prevents an adequate response to hopes and fears of the sick and of their families. The request to give free rein to destruction of embryos for research on embryo stem cells is nourished by hopes cultivated in these people. According to some, to impede this research would be equivalent to killing of our sick because it is culpable not to look for solutions to a disease when there is possibility on the part of those who must perform it.

The idea seems scientifically based, that research on non-embryonic stem cells offers concrete hope to respond to the legitimate concerns regarding health of people. This response is in accordance with ethical requirements. It would be a contradiction if science, which proposes to serve man and all mankind, was to pursue this scope, crushing innocent human beings and instrumentalizing human lives even if still incipient.

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