REPORT

On the use of stem cells in biomedical research and clinical medicine

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The purpose of the present report is to prepare the ground for a debate on the principles, which should govern the derivation and use of stem cells in biomedical research and in clinical medicine.

The therapeutic potential which the use of stem cells promises for a host of hitherto incurable diseases calls for the establishment of rules of ethics which will reconcile the specific biomedical developments with the fundamental ethical values of contemporary society.

The fact that the chief - though not the sole - source of stem cells are embryos derived either from artificial *in vitro* fertilisation or from terminated pregnancies brings us face to face with crucial ethical dilemmas. At the center of these dilemmas are differing views on the protection of human life, and, consequently of the life of the embryo.

On this issue, it is a well-known fact that two kinds of views have long been put forward. There are views of a 'metaphysical' grounding, according to which, human life deserves an absolute protection from the moment of its very first existence. There are also views of a 'conventional' grounding, according to which the degree of protection of human life depends upon the ideas prevailing, but nevertheless in a process of change, at a given time in society, and thus may vary with time and place. A consequence of ‘metaphysical’ views is skepticism towards any kind of use - and, of course, any possible destruction - of even the simplest form of human life (and certainly of the fertilised ovum). By way of contrast, ‘conventional’ views accept a 'ranked' protection of the different forms of life. They accept also the possibility, on certain conditions, of the use of some of these (particularly of the simpler sort) as 'means' for the serving of other values (for example, the protection of life or health of another individual). It is unavoidable that such conflicts of views on so fundamental an issue should be a continuing phenomenon, giving rise to constant questioning, which will inevitably be topical, because of the progress of scientific research in biomedicine. It is, however, obvious that to the specific question of

'whether' the use of embryos - and, by extension, of stem cells - is permissible there are three possible answers: no use is permissible, any use is permissible, or certain uses are permissible.

In order to facilitate the work of the Commission, we have thought it useful, in the first part of this report: (a) to clarify the biological potential of stem cells, depending upon the stage of development of an organism; (b) to describe the benefits which may be derived from the use of stem cells; (c) to explain the theoretical and practical limitations involved in their use and to identify alternative methods which may circumvent some of these limitations. In the second part, we have attempted to give a presentation of the legal framework currently in force, as that can be deduced from the relevant acts of legislation. In the third part, we have undertaken a summary of the ethical dilemmas which arise. Finally, we have attempted to formulate a certain deontological framework by which we have thought it desirable, in the light of what has gone before, that the derivation and use of stem cells should be governed.

Part One

1. Stem cells and the development of the embryo

In humans, upon fertilisation, the union of an oocyte (egg) and sperm produces the first zygotic cell, and it is the successive divisions of this which lead to the creation of a new organism.

In the first days post-fertilisation, the cells derived from the successive divisions of the initial zygotic cell, called blastomeres, are totally undifferentiated, have the capability of self-multiplication, and can give rise to any cell type of the embryo, including the membranes and tissues needed to support its development (e.g., the placenta). For this reason, blastomeres are termed totipotent stem cells. At day 3 post-fertilisation, the evolving organism (zygote) consists of eight blastomeres. During this early stage of development removal of one or more blastomeres does not affect the ability of the other blastomeres to develop into a fetus. In fact, if the developing zygote separates in half at this stage two identical twins will develop.

From the next stage, of 16 cells, the zygote, which is now called a morula, enters the uterine cavity, where it remains for another four days before it implants in the uterine wall.

Cell division continues, creating a cavity known as a blastocele in the center of the morula and the whole structure is now called a blastocyst. This morphological change of the zygote marks the first event of cell differentiation: the formation of an outer layer of trophoblast cells, which will give rise to part of the placenta, surrounding a group of about 20 to 30 inner cells (inner cell mass) which remain undifferentiated. At this stage, the inner cells can no longer give rise to all the cells necessary to form an entire organism. Thus they have lost a part of their totipotency and for this reason are now termed 'pluripotent' stem cells.

The outer layer of trophoblast cells secretes an enzyme which erodes the uterine wall, thus preparing the implantation site of the embryo. Once implantation has taken place, the zygote becomes an embryo.

In the week following implantation, the trophoblast and the underlying cells proliferate rapidly to form the placenta and of the other membranes which surround and nourish the developing embryonic cells. At the same time, the inner cells of the blastocyst divide rapidly to form the embryonic disk, which will eventually develop into the embryo. When 14 days post-fertilisation have elapsed, the embryonic disk consists of some 2,000 cells and the first organised development of the embryo is observable as the posterior-anterior axis is formed. In the six weeks which follow, the embryo grows and the main systems of the organism take shape. In general, as cells are further differentiated, they lose their capacity to enter developmental pathways which were previously open to them. At this point, two months of the embryo's development have been completed.

At the beginning of the third month, the embryo becomes a fetus. The following months –till birth- development is added to and the formation of the organs and tissues is completed. When development is completed, certain cells remain undifferentiated, retaining their capability of self-renewal, but showing relatively limited potential as to what types of differentiated cells they can produce. That is, they lose their pluripotency, although some of these undifferentiated cells are capable of producing a considerable

number of types of differentiated cell types. Such cells are now called precursor stem cells or simply stem cells.

The function of the stem cells found in the postnatal and adult organism is to keep constant the number of differentiated cells in tissues in which cells have been destroyed through injury, disease, or natural cell death.

Today, it is believed that in human adults there are about 20 different sources of precursor cells. We speak of them as sources of precursor stem cells because they cannot supply the same types of differentiated cells under normal conditions; that is, each source produces chiefly differentiated cells of the tissue in which it resides. In spite of this, it has been found that under experimental conditions adult stem cells are capable, if given the appropriate stimuli, of differentiation into cell types which they would not have produced under normal conditions. It would seem, then, that adult stem cells retain at least a part of their pluripotency.

Similar to stem cells, the primordial germ cells, located in the early reproductive system of the developing fetus, can be obtained from cadaveric fetal tissue after abortion. These cells, in normal conditions, function as supporters and precursors of the production of gametes, but when they are put in culture, it is possible for them to be re-programmed as pluripotent stem cells.

2. Possible use of stem cells

It is possible to distinguish three fields in which the use of stem cells is extremely promising in terms of medical applications.

In the field of basic research, the use of pluripotent stem cells could help in an understanding of the complex processes, which take place during embryonic development. In spite of the fact that we are aware that the process of cell differentiation is controlled by the activation and inactivation of certain genes, which these genes are or how they are activated or inactivated is not always known. The identification of the factors that determine the process of cell differentiation can help in the understanding of serious diseases which are due to abnormal cell differentiation and cell division (e.g., cancer).

In the field of pharmacology, the use of pluripotent stem cells could bring about a spectacular change in the way in which pharmaceuticals are developed and monitored. This is because the properties of new drugs could be tested on activated pluripotent stem cells, and thus on many different cell types, so that only those drugs which show themselves to be safe for cell development and have beneficial effects would receive a license for tests on animals or clinical trials in humans.

The most spectacular potential application of the use of pluripotent stem cells is the production of differentiated cells and tissues. Many diseases and disorders are due to the disruption of cell function or the destruction of tissues of the body. Today, donated organs and tissues are used to replace ailing or destroyed tissues. The activation of pluripotent stem cells so that they develop into differentiated cell types makes possible a renewable source of cells and tissues to be used as transplants and to treat many diseases and disabilities (e.g., spinal cord injury, strokes, heart disease, burns, Parkinson's and Alzheimer's disease, etc.).

3. Limitations

The basic limitation at present on the use of stem cells focuses on a lack of understanding of the mechanisms of cell differentiation. This means that before their systematic medical application can become a possibility, the use of stem cells will centre chiefly on the field of basic research.

Over and beyond this, however, the main interest in the use of stem cells is in the production of transplants. Thus, it is not only the problem of the programming of stem cells so that they can produce a specific cell type which must be solved, but also that of genetic histocompatibility of the tissues between donor and recipient.

To address the issue of histocompatability, two alternatives have been proposed. The first is the production of stem cells by the techniques of cloning and the second is the creation of cell lines or tissue banks representing at least the commonest types of the histocompatibility system.

The technique of cloning is based on the substitution of the nucleus of the egg by the nucleus of a mature somatic cell (somatic cell nuclear transfer). Since somatic cells

contain twice as many chromosomes as gametes (egg and sperm), the nucleus of a somatic cell contains all the genetic information needed for the development of an organism; that is, it replaces the fusion of the nucleus of the egg with the nucleus of the sperm.

If the development of this artificial zygote is allowed to be completed, the resultant organism will be genetically identical with the organism from which the somatic cell has been derived.

If the development of the embryo is interrupted at the blastocyst stage, pluripotent stem cells can be isolated which have the advantage over pluripotent stem cells of a different origin that the differentiated cells which can be developed will be genetically identical with the histocompatibility system of the donor of the somatic cell.

Nevertheless, this method is of no use in cases where the donor is suffering from some genetic disorder, since the pluripotent stem cells will carry the same defective gene or genes as the donor.

This problem could be circumvented by the creation of tissue banks from healthy donors which either represent the main genetic types of the histocompatibility system or contain genetic modifications of the genes of the histocompatibility system so that the rejection of transplants is prevented.

Part Two

The existing legal framework

At the legal level there are considerably different approaches, in respect to derivation and use of stem cells. In this part we report the legal choices adopted abroad (1) and we attempt an approach from the view of the existing Greek legal order (2).

1. A comparative presentation of the legal framework

As far as the "origin" of stem cell's derivation is concerned we detect three main trends.

(a) In some countries it is prohibited the creation of supernumerary embryos in vitro, from which stem cells could be derived, and even more the creation of embryos for research purposes solely. In Germany, for example, it is forbidden to create an

embryo that is not intended for immediate implantation, while in Ireland any supernumerary embryos created are transferred to the cervix of the woman where they are expected to perish. In Germany, research on the human embryo is only permitted when the embryo is not harmed and a pregnancy is still possible. It must be said that a similar provision includes also the European Convention on Human Rights and Biomedicine article 18.

(b) There are countries where creation of supernumerary embryos is permitted but remains prohibited the creation for research purposes solely. In these countries there are provisions determining the maximum time limits of embryo storage (cryopreservation) as well as provisions about their possible use. In Austria for example storage is limited to one year and embryos may only be used for implantation to the woman from whom the oocytes originated. After this time limit any stored embryos are destroyed. In other words, embryo donation either to other couples or to research is prohibited. In contrast, in other countries, human embryo research is permitted, subject to certain restrictions. There is a core agreement not to conduct research after embryonic day 14 and there is prohibition on *in utero* transfer of research embryos. However, there are differences concerning other specific restrictions. In Denmark all research projects are subject to the approval of an ethics committee and the purpose of the research must be the improvement of i*n vitro* fertilization (IVF) success rates. In Finland and Sweden research on human embryos is permitted, with the woman's consent and on the condition that research does not include genetic modification of the embryo. In France progenitor's consent is demanded while the aim of the research must be therapeutic for the embryo and the embryo is not harmed. In Spain research is permitted only for therapeutic or diagnostic purposes with progenitor's consent. Beyond these purposes, research can only be carried on non-viable pre-embryos with the aim to improve the artificial procreation techniques.

(c) Only two countries accept both the research on supernumerary embryos *in vitro* and the creation of human embryos solely for research purposes. In Britain recently has been adopted specific legislation regulating the derivation and use of

stem cells. Three new research directions on human embryos have been added to the permissible ones, under the Human Fertilisation and Embryology Act (1990), which concern the acquisition of knowledge about the development of serious disease as well as enabling such knowledge to be applied in relevant treatments. Prior to this amendment (January 2001) the Act permitted research related solely to reproductive issues. The new embryo research regulations anticipate the possibility of creating human embryos solely for research purposes given that research is conducted till day 14 post-fertilisation, with donor's consent and without financial inducement. In Japan with a law established in June 2001 research is permitted on supernumerary human embryos as well as creation of embryos by cloning (the technique of somatic cell nuclear transfer) for therapeutic purposes.

(d) It is worth noting that many countries announced recently that examine to institute relative legislation. President Bush in the U.S.A. announced that in order research on stem cells to be eligible for federal funding, stem cell lines had to be derived with donor's informed consent, from excess embryos created solely for reproductive purposes, without any financial inducement to the donors, and prior to the time of his announcement on August 9th, 2001. In Australia is under consideration the adoption of legislation that would permit both human stem cell research and derivation of stem cells from unwanted embryos created during fertility treatments. In Canada has been submitted a draft bill for all aspects of reproductive technology including embryo research, permitting research on supernumerary embryos but not the creation of embryos solely for research purposes. In Israel is considered the adoption of guidelines permitting both research on supernumerary embryos and the creation of embryos by cloning for therapeutic purposes. Finally in India is under consideration regulations that could include sharing of commercial benefits that emerge from stem cell lines between researchers and donors.

2. The legal framework in Greece

The adopted regulations and international trends concerning research on human embryos do not follow generally accepted rules that govern the derivation and use of stem cells. For the Greek legal order however, we could deduce in this connection general guidelines from other instruments already in force in the broader sphere of biomedicine.

This general legal framework is described below, as regards the *origin (2.1)* and the *use* of stem cells *(2.2)*

2.1. Origin of stem cells

2.1.a. Derivation from embryonic tissue

A prerequisite here is abortion, which in the Greek legal order was recognised by Law 1609/1986. The law does not make clear whether a person (e.g., the doctor or the spouse) other than the woman, to whom, in principle, the embryonic tissue derived from abortion 'belongs' as a 'part' or 'product' of her body, can have a right to the use of it. Apart from this, to the extent that abortion may be a woman's free choice up to the completion of the twelfth week of pregnancy, a question arises as to whether the woman can consent to have an abortion with a view to the embryonic tissue then being used to obtain stem cells, perhaps even with provision for a financial consideration.

2.1.b. Derivation from an embryo in vitro

Embryonic stem cells can also be obtained from embryos of the first days following fertilisation of the egg; these are kept in a suitable laboratory environment and are usually 'surplus' to a process of artificial procreation. Here the case differs, because the intervention is on a living organism, which can potentially develop into a 'complete' human being.

In this case, in the Greek legal order, Law 2619/1998 is applicable. This ratified the Convention of the Council of Europe on Human Rights and Biomedicine (Oviedo 1997). By its incorporation into Greek law, moreover, this convention binds any future options of the Greek national legislator, according to the article 28, par. 1, of the Constitution.

Article 18 of the Convention includes specific provisions on "research on embryos *in vitro*", in accordance with which:

"1. Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo.

2. The creation of human embryos for research purposes is prohibited."

These provisions also cover, in general terms, the instance of the derivation of embryonic stem cells from embryos preserved *in vitro*.

One procedural and two substantive restrictions are observable here. The procedural restriction lies in the fact that research on embryos *in vitro* has to be expressly permitted by a specific law. Thus, the national legislator is not permitted to remain 'indifferent', that is, to rely on general provisions of law in order to deal with the matter, but needs to ensure that its various manifestations are covered by specific legislation. The derivation of stem cells does not, of course, in itself constitute 'research'. Nevertheless, from the provision's *ratio* - the "adequate protection of the embryo" - it can be deduced that this covers any intervention on the embryo carried out for research purposes.

This mandate has, however, significance simply as a guideline for the action of the legislator. The fact that at present there is no such specific legislation does not mean that the derivation of stem cells is 'illegal' or that it falls into some gap of the law: The fact that the legislator remains inactive does not entail the inertia of the law in general. Thus, the general rules on the protection of the personality (Article 5, para. 1, Constitution; Article 57, Civil Code) are also applicable here: to the extent that embryos can be regarded as 'products' of the body and elements of the personality of those who have provided the gametes, their use depends upon the will of the latter. However, to the question of whether the will of a third person can determine this use, no answer is supplied by the legislation.

Furthermore, the two substantive provisions - on the adequate protection of embryos and the prohibition of the creation of embryos for research purposes - of Article 18 of the Convention are applied regardless of the fact that there is not yet specific legislation. This

is because if it is to be supposed that their application depends upon the introduction of this special legislation, the legislator of Law 2619/1998 would appear not to wish its own regulations to have force before the occurrence of what is in principle an uncertain event. He would thus have appeared, in the last analysis, not to be legislating - which is, naturally, absurd.

2.1.c. Derivation from persons

It is also possible for stem cells to be removed from the reserve, which every human being possesses throughout his/her life for use in the renewal of tissues either of themselves or of another person.

The former instance presents no particular legal problems. In the latter, however, the terms and procedure for the taking of stem cells need clarification. It should be noted that in this case Law 2737/1999 on "transplants of human tissues and organs" could not be applied, since, on the basis of scientific terminology, stem cells cannot be included within the concept of 'tissues'. However, Law 2619/1988 (Convention on Human Rights and Biomedicine) is applicable here, to the extent that it stipulates general regulations for interventions in matters of health (Articles 1-10 of the Convention). To these regulations should be added the general provisions of Greek law on the protection of human value (Article 2, par. 1, Constitution) and personality (Article 5, par. 1, Constitution; Article 57, Civil Code) and the relevant provisions of the penal legislation (e.g., Articles 308 *et seq*. of the Penal Code on 'bodily harm'). Where the stem cells are likely to be taken from a minor, the provisions of family law dealing with parental duties are also applicable.

2.2. Use of stem cells

The use of stem cells after derivation, during culture, and the attempt to 'orientate' their differentiation capacities is, basically, a matter with no special legal importance.

A use which is chiefly of interest to the law is the transplanting of the tissue which has been obtained in this way to an animal or human being when, on scientific criteria, the method involved is still at the experimental stage.

2.2.a. Use on animals

Experimental use of stem cells on animals must be carried out in accordance with the rules stipulated by Law 2015/1992 (Convention of the Council of Europe on the protection of vertebrate animals used for experimental or other scientific purposes).

2.2.b. Use on human beings

Here Law 2619/1998 (Convention on Human Rights and Biomedicine) is again applicable. In Chapter V of the Convention (Articles 15-17), specific terms for the protection of the individual in cases of biomedical experiments are provided. These terms can be summarised as: (a) the guarantee of the effectiveness of the research; (b) the implementation of the principle of proportionality; that is, the avoidance of risks disproportionate to the expected result; (c) a guarantee of the merit of the particular research project; (d) the express, specific, documented, free, revocable, and informed consent of the person involved. Furthermore, in the case of those not in a position to give their consent, it must be ensured that (a) there will be a real and direct benefit to the condition of health of these persons; (b) research cannot be carried out with comparable effectiveness on individuals who are capable of giving their consent; (c) there is written and specific authorisation to the representative by the person involved; (d) the person concerned does not object.

Part Three

From the account given of the legal framework currently covering the matter, it is obvious that many ethically crucial aspects of it remain without clarification. This is understandable in the light of the fact that it is only recently that research in this particular field has begun to be the object of public debate. What is therefore required is that certain basic ethical dilemmas should be confronted and that a deontological framework in the matter should be distilled, to facilitate the interpretation of areas which remain unclear in the law or to provide the argumentation for a future legislative initiative.

Differences in the moral evaluation of the embryo

There are three main views concerning the moral status of the embryo.

1. Full personhood.

The human embryo has a moral status equivalent to that of an adult human being from the moment of conception. This is mainly the position of the Roman Catholic Church and its consequence is that there is a firm opposition to any type of research involving human embryos, irrespective of the stage of embryonic development. This moral position opposes to stem cell research which involves destruction of the human embryo. Such a policy has the advantage of establishing a clear deontological norm. The main disadvantage though is that it leads to lack of competitiveness; since research on human embryos is not prohibited universally, scientific research and certain clinical practices are just displaced to other countries. Furthermore, such policy retains its moral and rational integrity only if prohibits the use of medical derivatives and products that have been developed from research on human embryos, as well.

2. Gradual moral status

The developing human embryo acquires progressively moral status, as gestation proceeds, but this is never equivalent to the moral status of a living child or adult. This is the position adopted by both the Warnock Committee in UK and the Ethics Advisory Board in the US Department of Health. Those who hold this perspective accept time limits, such as day 14^{th} post-fertilisation (the emergence of primitive streak, individuation) or day 18^{th} (beginning of neural tube development) or day 22^{nd} (onset of fetal heartbeat) constraining embryo research. These time limits are considered to define the acquisition of moral status of the embryo. However this moral point of view does not necessarily embraces the position either that embryos are commodities or that can be created for research purposes solely. Certain professional associations (i.e. E.S.H.R.E.= European Society of Human Reproduction and Embryology) accept the creation of human embryos for research purposes in extremis, that is, when research cannot be conducted on animals or supernumerary embryos. The constraints in embryo research adopted by such policies concern not only the time limits for embryo destruction but also

research orientation and / or the conditions of implementation. The establishment of bioethics committees that control and supervise research activities, the restriction of funding and/or the prohibition of patents on products derived from human embryo research are some ways of control for research activities involving human embryos, in order to attain social acceptance.

3. Embryo as property

The human embryo has no specific moral status and should be treated as commodity, which is the property of the progenitors. This point of view is depicted in some judicial rulings in the USA and Australia. This position, undoubtedly "clear" from a moral point of view, holds that research on human embryos must not be restricted and that embryo commercialisation is permitted. Commercialisation without restrictions though could lead to situations of direct exploitation of the donors. Furthermore such a policy is susceptible to raise social mistrust towards the methods adopted by the scientific community in order to achieve its objectives.

The deontological framework

Based on the above-mentioned moral positions it is possible to propose a deontological framework. We adopt the point of view of the gradual moral status for the human embryo and we formulate certain deontological principles about stem cell research, taking into account their origin and uses. We envisage certain constraints for scientific research conditions, orientation and funding.

A. Origin of the stem cells

a. Following abortion

1. The removal of embryonic tissue following an abortion is permissible, provided the consent of the woman who was pregnant is obtained. Even if the embryo in the first stages of development - when freely-chosen abortion is acceptable - cannot be regarded as a 'person', that is, a 'subject' of independent value in a

society governed by the rule of law, it is, however, a component of the woman's personality, a quasi 'part' of her body. As such, must be dependent absolutely upon her will. Arbitrary use of embryonic tissue by anyone, following an abortion, would lead to an affront to the woman's personality and for that reason should be precluded.

2. Since the embryo is a component of her personality, the woman's consent should be sought after she has been properly informed of the specific use of the embryonic tissue. This information should be provided by a specialist scientist and should also include the source of financing of the research, so that any possible commercialisation can be avoided.

3. In spite of the fact that the spouse, partner, or the specialist who carries out or is informed of the abortion may have a reasonable interest, whether emotional or scientific, the fact that the embryonic tissue constitutes a component of the woman's personality does not allow them to be recognised as having a say in its fate; it must be the woman's decision which determines this. This may be certified by the introduction of a written form of consent.

4. It must be ensured that the embryonic tissue does not come from an embryo which was created for research purposes. An agreement on this on the part of the woman, before or after conception, may conceal direct exploitation of her person (as a 'means' for research) and thus an infringement of her value as a human being, particularly as pregnancy entails a significant burden on the functions of the organism. It would be correct to prohibit such agreements expressly, with the corresponding penal sanctions. These sanctions would, of course, be more severe where the agreement included provision for a financial consideration, since that further intensifies the impression of the exploitation of the person involved.

5. In special cases of gestation termination for medical reasons, research on embryonic tissue is desirable since it might eventually lead to elimination of this type of abortions. Such a research promotes scientific knowledge about the causes of anomaly which might be introduced in the form of prenatal diagnostic tests or

preimplantation diagnostic tests when the woman or the couple has used the technology of assisted reproduction.

b. From an embryo in vitro

1. The derivation of stem cells from an embryo *in vitro* gives rise to very serious ethical dilemmas. There can be no doubt that the 'use' for research purposes of a 'life-bearing' entity which is distinguished by its capability to evolve into a 'complete' human being on certain conditions, brings into play the reflexes of a society built on the basis of respect for the value of human beings.

2. Nevertheless, it is equally certain that no capacity of being a 'person' can be ascribed to an embryo in such a way as to recognise to it a value comparable with that ascribed to every human being. This does not seem to be disputed - at least at present - in contemporary societies, and for that reason practices such as abortion and scientific research are regarded as morally acceptable. This basic position is treated as a commonplace of modern European civilisation *par excellence* by the Convention on Human Rights and Biomedicine of the Council of Europe, which recognises, on certain conditions, research on embryos. Any thinking on the ethics involved cannot ignore this minimum assumption, even if it has doubts about its completeness. Therefore it is reasonable today that the Convention's principles should be taken seriously into account in dealing with the particular issues raised by research on embryos and, more specifically, the derivation of stem cells from them, without, however, this limiting the scope of the ethical discuss.

3. Within this general framework, the distinction between totipotent and pluripotent stem cells, as defined above, stands out as ethically crucial. It is possible from the culture of totipotent stem cells - taken from the embryo of the first three days - for not merely tissues, but complete organisms, identical with the embryo of origin and between themselves, to result. In this way a new technique of procreation, which would, however, lead to the creation of human beings identical as to their external characteristics (following the model of reproductive cloning) could be developed in the future. This prospect is ethically questionable, because the fact

of artificially sought, and not chance (as in the case of monozygotic twins), identity would be a life-long impediment to the free development of the personality and, more generally, the autonomy of these human beings: the individual identity of their personality, their 'difference', would not be a given, but would constantly have to be proved. In the last analysis, it is impermissible that such a burden should exist in a society which respects human value. For this reason, it would be more acceptable, from a moral point of view, for the removal with the purpose of culture of totipotent stem cells to be expressly prohibited.

4. It is again essential that the written consent of the donors of the gametes from which the embryo was derived - since it is an element of their personality - should be obtained after they have been properly informed of the specific use and source of financing of the research. This information must be given together with a certified confirmation: (a) that the embryo will not be used for reproductive purposes of third parties; (b) that any refusal of consent on the part of the individual involved will not have unfavorable consequences for future needs in terms of medical treatment.

5. For the reason of possible exploitation of the donors by third parties, as in the case of embryonic tissue, here too the possibility of agreements on the removal of stem cells with a financial consideration should be precluded.

c. From individuals

1. The removal of stem cells from individuals also presupposes the individual's prior free consent, with the guarantees already prescribed in detail by the Convention on Human Rights and Biomedicine. However, the prohibition of the removal of stem cells from minors for experimental purposes should also be examined.

2. For the same reason as in the two preceding instances, the possibility of concluding agreements in the matter with a financial consideration should be expressly prohibited.

3. In order to safeguard the independence of the donor of the stem cells and of the possible recipient of the tissues produced from them, it would be proper for the anonymity of the donor to be maintained, as in the case of transplants.

4. The production of stem cells by the technique of somatic cell nuclear transfer presupposes the creation of an embryo. If the embryos concerned serve exclusively for therapeutic purposes and there is no alternative therapeutic technique, their creation should not be precluded. In any event, however, the death of the donor of the somatic cells should entail the destruction of the embryos to preclude the possibility of reproductive cloning.

B. The use of stem cells

1. The experimental application of research into stem cell to animals should follow the basic principles of environmental deontology. The avoidance of pain and the necessary sparing use of experimental animals should be a constant concern of specialists and should be absolutely paramount when the effectiveness of the research is not adequately predictable. These principles are already included in the law 2015/1992, but it would nevertheless be right for them to be included and further developed in a *ad hoc* code of ethics on the use of stem cells, in order to ensure commitment on the part of researchers.

2. Recipients of tissues which are derived from stem cells should be protected from the possibility of their transformation into objects of research. The Convention on Human Rights and Biomedicine, in particular, contains the basic principles required to safeguard individuals from this risk (see above).

C. Control procedures and conditions for research projects

Any research project must be submitted to the control of a specialized agency, according to the relevant British or French model. Furthermore, the respect of the principle of proportionality (according to which a research cannot overcome its particular goal) and of the precaution principle (which demands for any research a prior evaluation of the risks)

must constitute the core subject of this control. In the cases of "banks" where embryonic tissue is stored, there is also an important need for the personal genetic data of third persons genetically related to an embryo to be protected.

D. The financing of research projects

The State should elaborate a funding policy for stem cell research after broad consultation with the private and public research bodies taking into account the proposed deontological framework. Stem cell research is crucial for achieving medical progress while the risk of unfair commercialization of research products demand a policy of specific incentives rather than a policy of repressive control.

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