The subsidiarity principle in the context of embryonic stem cell research

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Embryonic stem cell research is regulated by different forms of the subsidiarity principle, i.e. research on embryos should only be conducted if no suitable alternatives exist. Four types are discussed: animal versus human material, adult versus embryonic stem cells, affected or at risk embryos versus healthy embryos, and supernumerary versus research embryos. Three major arguments regarding the subsidiarity principle are discussed: the necessity argument, the least offensive moral approach and the ‘nothing is lost’ argument. It is proposed that the burden of proof should be shifted onto those who oppose embryonic research. When the freedom of research and the moral obligation to relieve human suffering is taken seriously, the opponents of this research should first demonstrate that embryonic stem cells do not work or that adult stem cells work better.

Key words: embryo/ethics/research/stem cells/subsidiarity

Introduction

Stem cells are considered to have great therapeutic potential. Researchers all over the world emphasize the enormous possible benefits stem cells may have for the treatment of diseases. However, stem cell research projects are considered morally problematic when the source of the stem cells is the human embryo. Two general conditions govern the instrumental use of embryos: (i) the proportionality principle, i.e. the destruction of the embryos should serve important and worthwhile goals and purposes (generally implying medical therapy); and (ii) the subsidiarity principle, i.e. research on embryos should only be conducted if no suitable alternatives exist (de Wert et al., 2002).

Both principles can be found in legislation regulating embryo research. When we restrict ourselves to subsidiarity, the following examples can illustrate the importance attached to the principle by the law makers. The new Belgian ‘Law on research on embryos in vitro’ contains two clauses which illustrate the subsidiarity principle. Art.3, §6 states that research on embryos is allowed if no other research method exists that is equally effective. Art 4, §1 stipulates that the creation of embryos for research is forbidden except when the goal of the research project cannot be reached through research on supernumerary embryos. Legislation in other countries contains similar clauses. Section 10b of the Dutch ‘Act containing rules relating to the use of gametes and embryos’ (Embryos Act) says that the Central Commission shall only deliver a favourable recommendation on a research protocol when it can reasonably be assumed that the insights cannot be achieved through any form or method of research other than research with the embryos in question or through a less invasive form of research. In the UK, schedule 2, paragraph 3 (6) of the ‘Human Fertilisation and Embryology Act 1990’ states that no licence … shall be granted unless the Authority is satisfied that any proposed use of embryos is necessary for the purposes of the research’. This paper analyses the subsidiarity principle and its implications in the context of the recent debate on embryonic stem (ES) cells.

Subsidiarity in research

For subsidiarity to serve as an action guiding principle, we should be able to determine what suitable alternatives are. Suitable alternatives from a moral point of view are entities (or material of entities) with a lower moral status. This principle, in combination with a number of other conditions imposed on research such as the limitation to therapeutic goals, is designed to express the respect due to the entities and establishes an order of priority. In the context of stem cell research, four arguments are based on the principle: (i) research should first be done on animal material; (ii) adult stem (AS) cells should be used before ES cells; (iii) affected or at risk embryos should be used before healthy embryos; and (iv) supernumerary embryos should be used before research embryos are created.

Animal versus human material

A well established hierarchy in medical research, although increasingly debated, is that experiments should first be
conducted on animal material. Extensive animal research should provide a sound basic scientific understanding as an adequate foundation before entering clinical trials (Khushf and Best, 2002). This step presumably decreases the need for research on embryonic cells and indirectly implies a moratorium on research on embryos. For two decades, research has been carried out on mouse ES cells. Derivation, characterization, and differentiation of mouse ES cells have been studied extensively and served as a model for human ES cells studies. However, comparison of markers of mouse and human ES cells revealed substantial differences between these two types of ES cells. Furthermore, if human ES cells are to be used in the future for treatment, they need to fulfil the requirements of cell therapy in patients. This means that derivation of ES cells has to be done under strict conditions of safety which can only be determined if these conditions are established on human ES cells. For instance, safety conditions have to be worked out for the derivation process itself before established ES cells will be used in therapy. There is no animal model available that enables researchers to reach this goal. Similar arguments apply to the characterization and differentiation of all human ES cell lines which are candidates for therapeutic cell therapy. In short, animal research does not eliminate the need for experiments on human material since research will have to be done on human embryos anyway before clinical application can even be considered. Moreover, when embryonic material is abundantly available from supernumerary embryos, basic research on these cells may speed up the process and can run parallel with animal research.

**Adult versus embryonic stem cells**

Also within the field of human cell research, a ranking should be established since there are several alternatives for ES cells, i.e. AS cells, stem cells from the umbilical cord and fetal primordial germ cells.

A major problem for the application of the subsidiarity principle on adult versus embryonic cells is that one cannot predict with a reasonable degree of certainty which paths are the most promising to reach the goals. This lack of information makes it difficult to foresee future developments. This is a problem for both sides in the debate. The Pontifical Academy for Life (2000) of the Roman Catholic Church states that ‘adult stem cells represent a more reasonable and human method’ although they themselves admit in the very same sentence that ‘many further steps in both areas are necessary before clear and conclusive results are obtained’. Without their ethical objections, they have no reason to prefer AS cells, much less to forbid the use of ES cells. Unless they have access to a privileged source of information, there is no firm ground at present for the claim that AS cells are more promising. The lack of knowledge greatly weakens the usefulness of the subsidiarity principle. It can only function well (in expressing moral status) if proof has been given that alternative methods may do the job equally well. At present, the situation strongly resembles a catch 22: scientists must demonstrate that ES cells are better than AS cells but they are not allowed to do research to prove this until it has been shown that ES cells are better.

It is worth mentioning at this point that a basic presumption underlying the subsidiarity principle is that embryo research is permitted in principle. The discussion is not about whether or not embryo research can be done but only in which circumstances and in what order. As a consequence, those who oppose all types of embryo research are not entirely honest when they appeal to the subsidiarity principle. In 2001, a group of physicians, scientists, theologians and others published a statement in favour of AS cell use. At the end, they concluded: ‘However, even if such methods do not prove to be as valuable in treating disease as are human embryonic cells, use of the latter in the name of medical progress is still neither legally nor ethically justifiable for the reasons stated in this document’ (Anonymous, 2001). These opponents are not really interested in the comparison of the efficacy of the different stem cell types. For them, the subsidiarity principle merely serves to postpone research on embryos endlessly and thus comes down to a full prohibition.

**Affected versus normal embryos**

Recently, Pickering et al. (2003) have presented the use of embryos surplus to therapeutic requirements following pre-implantation genetic diagnosis (PGD) as an ethical alternative for the procurement of research material for stem cell derivation. Three categories of embryos are considered: a) embryos in which a specific diagnosis is not available, but which are considered at high risk for transmitting a particular disease and are therefore unsuitable for replacement. This category includes the embryos diagnosed as male following PGD for X-linked disorders (only 50% are affected by the disease); b) a variable proportion (up to 30%) of embryos for which a diagnosis could not be reached due to failure of the diagnostic test in the biopsied cell; c) a proportion of embryos (up to 10%) classified as homozygous affected for a single gene disorder which may, in fact, be heterozygous.’ (Pickering et al., 2003). These categories illustrate that the hierarchy among the embryos is not solely determined by being affected or not but also by the risk of being affected. The higher the risk, the lower the acceptability of replacing the embryo in the woman for reproduction and the lower its moral status. Risk, however, has the disadvantage of being a continuous criterion. It immediately raises the question of how high the risk should be before the embryos shift to the category ‘unsuitable’. In addition, other continuous criteria such as embryo quality could be adopted for the same purpose. Although few criteria exist that allow us to predict with certainty that an embryo when replaced will not make it to a person, a selection is made and some embryos are neither replaced nor frozen because it is estimated that it is unlikely that they will be progressive or able to survive the cryopreservation (Pickering et al., 2003). In summary, two criteria could be added to establish an order of priority for research: (i) research should first be conducted on affected or at risk embryos rather than on healthy embryos; and (ii) research should first be conducted on low quality embryos rather than on top quality embryos.

If only affected embryos are used for stem cell research, people who accept the ‘nothing is lost’ principle should accept their use, since these embryos are, for all practical purposes,
unsuitable for reproduction. Moreover, the creation of stem cell lines from such embryos may have a number of important advantages. Such cell lines could enable the production of useful models for the investigation in vitro of disease pathogenesis (Hovatta and Ahrlund-Richter, 2001). At the Research Centre Reproduction and Genetics of the Brussels Free University, a research project was started that aims to establish and characterize ES cell lines from both normal frozen embryos donated for research by patients who underwent assisted reproduction treatment and embryos affected by genetic diseases as diagnosed by PGD. Once the cell lines are established, the studies will focus on the study of dynamic mutations as well as on genomic imprinting. Research may result in increased understanding of diseases such as cystic fibrosis. A similar reasoning underlies the idea of generating nuclear transfer ES cell lines from patients of known disease susceptibility (Pera, 2001).

It would be premature at present to restrict research on ES cell lines to low quality embryos. According to some, the success rate of cell line production is very high if morphologically normal blastocysts with obvious inner cell masses (ICMs) are selected (Trounson, 2001). Others, nevertheless, managed to develop stem cell lines from embryos that would have been discarded because of poor quality (Mitalipova et al., 2003). Further research is needed to determine whether low quality embryos make poorer stem cells.

Supernumerary versus research embryos

The question of the relevance of intention has divided ethicists and physicians; is it ethically relevant whether the embryo was created with the intention to procreate or whether it was created solely for research purposes? (Devolder, 2005). Regardless of the philosophical answer, the rule that supernumerary embryos should be used before new embryos are created is basic rationality. Why create new material when there is an abundance of useable material? Between 1991 and 1999, 53,497 surplus embryos were donated for research in the UK (House of Lords, 2002). In the Research Centre Reproduction and Genetics of the Brussels Free University, ~1500 frozen embryos are available for research. Since storage capacity becomes an issue at some point, the centre obviously prefers to do research on stored embryos. Moreover, scientists do not create embryos just for fun or sheer malice. If they create new embryos, it is either because no supernumerary embryos are available or because the research goal cannot be obtained in any other way. This solution is used very sparingly. The Select Committee report of the House of Lords in the UK mentions that 118 embryos were created between 1991 and 1998 to study the techniques of freezing eggs, ICSI and the use of spermatozoids (House of Lords, 2002). In the Research Centre Reproduction and Genetics, research embryos were made to check the feasibility of some applications of PGD (Liu et al., 1993). In the preclinical phase of PGD for monogenic diseases such as cystic fibrosis, it was mandatory to establish whether a reliable and efficacious diagnosis of, for example, the ΔF508 mutation could be established on single cells and in particular on single blastomeres which were biopsied from 8-cell day 3 embryos. Reliability and efficacy needed to be established before applying PGD clinically. For that purpose, 14 research embryos were made by injecting donated oocytes with a single sperm from a donor who was an unaffected carrier of the ΔF508 mutation.

It is still unclear how many embryos will be needed for stem cell research and for the therapies that will eventually be developed. The Nuffield Council on Bioethics (2000) stated that ‘not all people wishing to donate embryos need be invited to donate them for the purpose of creating immortal stem cell lines as only very few embryos donated for research would actually be needed for such a purpose.’ On the other hand, when somatic cell nuclear transfer (SCNT) is accepted and proves safe, a relatively large number of embryos may be created to obtain immunologically compatible material for transplantation.

Necessity

The position expressed in the subsidiarity principle relies on one question: can the same result be reached by other means? Research is necessary in the strong sense if experiments on embryos are the only way to obtain the knowledge (Holm, 2001). However, the condition can be mitigated by specifying the questions: how fast can the goal be reached? How safe and easy is the treatment method? A technically difficult and risky cure may be found for Parkinson’s disease by 2020 if research is conducted on AS cells only, while a relatively easy method with high efficiency may be found by 2015 if research is done on ES cells. Would the earlier availability and the higher efficiency justify the use of embryonic material? If the use of embryonic material turns out to be safe and effective, a difference of 5–10 years will affect millions of people and their families (Fletcher, 2001). The Royal Society (2000) thinks that research on human ES cells will provide us with effective therapies more quickly, but adds that it is difficult to make predictions given the lack of knowledge. This knowledge deficit leads to different appreciations: the UK Department of Health (Department of Health, 2000) and the National Bioethics Advisory Committee (USA) clearly do not hold the same opinion on whether a particular type of research is necessary at the present time for the field to progress (Holm, 2001). The current lack of knowledge regarding the workable lines of research presents both opponents and proponents of embryo research with the opportunity to select those bits of information that corroborate their position. A low moral status of the embryo combined with a firm belief in medical progress will tip the balance in favour of embryo research, while a high moral status in combination with doubts about the projected benefits will result in a prohibition.

Other criteria to determine which cells should be used, besides necessity, are speed of progress, possibilities of the alternatives, foreseeable benefits, technical easiness, safety and security of the application for the patients, extent of the field of application (the number of diseases that can be treated), etc. Several technical aspects should be included in the comparison between stem cell types such as ‘the ease with which they can be made to multiply in culture, their longevity in culture, the range and nature of the mature cell types they can be induced to
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make, and the molecular signals that bring about these changes’ (European Science Foundation, 2001). de Wert concluded that ‘a multidimensional analysis, including the possibilities and risks of the alternative methods, is needed’ (de Wert et al., 2002). Moreover, such an analysis will show that it is unlikely that there is ‘a single approach to the use of stem cells in therapy: different disorders are likely to require different types of stem cells and different therapeutic approaches’ (House of Lords, 2002). When a sufficient amount of stem cells can be found in the adult, as for instance for haematopoietic stem cells, it is unlikely that embryonic material will be used.

The decision about the use of SCNT can illustrate this point. The main reason for using SCNT is that ES cells will be obtained which have the same genetic constitution as the person who will be treated. This eliminates the risk of immunological problems and graft-versus-host disease (European Group on Ethics in Science and New Technologies, 2000). This considerable advantage could be obtained without the creation of an embryo by SCNT if it proves possible to alter ES cells grown in culture immunologically to prevent rejection after engraftment or if AS cells of the person can be modified and reprogrammed to obtain the necessary cells. Whether the creation of embryos to obtain ES cells for treatment is justified depends, among other things, on the difficulty, safety and efficiency of modifying other cells to prevent rejection. Moreover, if the alteration of cultured ES or AS cells does not prove possible, years have been lost in which knowledge and expertise on SCNT could have increased.

The least offensive moral approach

Another aspect of the subsidiarity principle is expressed in the ‘why not take the least offensive moral approach’ (Doerflinger, 1999; Fletcher, 2001). If the same results can be obtained by two types of research, one should perform the research that is least offensive or least problematic. Evidently, a lot depends on who decides what the least offensive or least problematic approach is. Performing burdensome and risky operations on adults in order to obtain stem cells of a certain tissue may be judged more unacceptable than using ES cells. While for some types of cells (such as bone marrow) we are talking of pain and discomfort, for other types (such as neuronal cells) there are significant risks to the donor from the brain biopsy procedure (National Bioethics Advisory Commission, 1999). Harm done to actual sentient persons carries, according to most moral theories, much more weight than harm done to possible non-sentient persons. Those who appeal to the ‘least offensive approach’ argument assume wrongly that there is consensus on which approach is the least offensive. They seem to reason from a one-dimensional approach: every alternative which does not use embryos is a priori superior (de Wert et al., 2002).

If AS cells and ES cells would offer exactly the same possibilities and if they would be equal in all other aspects, AS cells should be preferred. When some people have moral problems with research on embryos and this research yields no real advantages compared with experiments that are inoffensive to those people, insisting on research on embryos is mere provocation. However, the reticence or consideration shown for the moral views of some cannot oblige the others to refrain from research on embryos. The moral offence to those who accept the full humanity of the embryo should be balanced against the potential benefits for future sufferers (Siegel, 1999; Meilaender, 2001). Some people are deeply offended by homosexual behaviour, but that does not mean that such acts should be forbidden or restricted. In our present society, we see no reason to adapt social life to people who hold these beliefs. In the same way, people who believe that embryos are full moral persons should not be able to dictate the research agenda of the whole community. They have already managed to put researchers into a defensive position (McGee and Caplan, 1999). In our opinion, the proponents of embryo research ceded too much ground to these groups. Society should, on the contrary, turn the table and put the burden of proof on those who oppose embryo research now. This position, which is consistent with the general attitude towards science and medicine, is based on the priority attributed to the principle of beneficence (expressed in the development of life-saving treatments and efforts to diminish suffering) and to the freedom of research. In that scenario, it should be proven that ES cells hold less promise than AS cells or that the ES cells cannot be used (because they, for instance, prove to be tumorigenic) instead of the other way round. In fact, given our duty to develop therapies to alleviate suffering, research should be conducted on those cells which are most likely to yield superior therapeutic benefits.

The ‘nothing is lost’ argument

In the majority of countries, when a couple no longer needs the embryos for their own parental project, they can choose between donation to others, donation for research (followed by destruction) and destruction (Pennings, 2000). There are other possible options but these are not considered acceptable in most legislations. It has, for instance, been argued that all supernumerary embryos after IVF should be donated to other couples (as the Spanish law stipulates) or that embryos should be cryopreserved indefinitely (as in Brazil). However, when couples are allowed to donate their embryos for research or dispose of them for destruction, the embryos are bound to be discarded and will die in any case. ‘Nothing is lost’ by destroying the embryos that had not already been lost with the decision of the parents (Outka, 2002). The use of the embryos for research determines how the destruction occurs but not whether it will occur (Childress, 2002). On the other hand, this justification for using embryos for research obviously disallows the creation of embryos for research. The principle has also been expressed as the ‘doomed embryo’ rule (Zoloth, 2002). It emphasizes the idea that flushing supernumerary embryos does not respect them more than employing them for research. In the latter case, at least something good comes from it. The same reasoning underlies the decision making of couples who do not want to donate to others; they frequently prefer the possibility of donation for research to simple destruction.
When someone argues that frozen supernumerary embryos should not be used for research, he states that continued cryopreservation is ethically superior to using them for research now (Annas et al., 1999). This position is difficult to explain if he accepts that the embryos are discarded anyway. Moreover, given these premises, there is no reason not to use cryopreserved embryos for research now, even when there are alternatives.

The reference to the alternative fate of the supernumerary embryos, i.e. destruction, is rejected by most opponents of research on embryos. Fletcher, for instance, argues that the idea that embryos can be used to derive stem cells because they will not be replaced anyway is based on the ‘theory that it can be morally right to kill a doomed human being to benefit others’ (Fletcher, 2001). In a similar vein, other people consider embryos as full human beings and consider embryo research as the use of one group for the benefit of another group (Anonymous, 2001). For these authors, apparently, there is no difference between a person and an embryo. Couples who discard their embryos because they no longer want to use them for their own reproduction are killing their children. The counterintuitive character of this idea is a strong indication that embryos are not given and should not be given the status of human beings.

**Conclusion**

The subsidiarity principle has several dimensions which allow a continuum of positions about research: postponement (a short or long moratorium), selection of types of embryos (super-numerary, affected or research embryos) and research goals (therapeutic purposes).

Given the huge potential benefits of stem cell research, all lines of research should be pursued simultaneously. Only then will it be possible to determine whether AS cells have more potential than ES cells or fetal germ cells. Arguing from the idea of the embryo as a person, the opponents of embryo research put the burden of proof on the scientists who defend embryo research. However, when freedom of research and the obligation to relieve human suffering is taken seriously, it is up to the opponents to show that ES cells do not work or that AS cells work better.

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