Use and Abuse of Empirical Knowledge in Contemporary Bioethics: A Critical Analysis of Empirical Arguments Employed in the Controversy Surrounding Stem Cell Research

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Introduction

In two articles about the controversy surrounding stem cell research,[1,2] Søren Holm claims that no argument has so far been advanced in the debate to justify the *necessity* of destructive research on human embryos for the therapeutic potential of stem cell research to be achieved, and that it is up to the scientists themselves to produce "convincing arguments" for their case.[3] This seemingly defeatist statement on behalf of bioethics originates from the viewpoint that neither a reiteration of old arguments about the moral status of the human embryo nor the generation of new arguments of the same kind are likely to have any positive bearing on the controversy; on the other hand, the impact of science on the current debate is unquestionable, due to three "partially independent" developments:

1. the invention of methods for derivation and in vitro cultivation of human embryonic stem cells (ES-cells)
2. the invention of techniques for cell nuclear replacement (CNR)
3. the publication of several studies suggesting that adult stem cells are in possession of a much higher *plasticity* than previously believed.[4]

This paper has three aims. The first is to identify different forms of empirical arguments employed and to critically assess their function in the debate. The second aim is to show that not only is there insufficient scientific evidence available to therapeutically justify human embryonic stem cell research but the same holds true for the opposite case; that is, of using therapeutic arguments to question the necessity of human embryonic stem cell research. Finally, I want to draw attention to a set of empirical arguments that seem to meet Holm's requirements of justification for allowing destructive stem cell research on human embryos. To facilitate the differentiation of empirical arguments employed in the debate, I will rely on the categorization of research in a report on stem cell research issued by The Select Committee, House of Lords, United Kingdom, on 13 February 2002 into:

1. basic scientific research
2. preclinical studies
3. large-scale clinical trials.[5]

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Types of Empirical Narratives Employed in the Debate

The Overstated Way of Storytelling

Holm's main critique against the protagonists of embryonic stem cell research is that their position is based on unwarranted empirical premises:

> The benefits that are put into the balance to justify the sacrifice are mainly the therapeutic potential promised by stem cell therapy. The public presentation of the benefits of stem cell research has often been characterized by the promise of huge and immediate benefits. As with many other scientific breakthroughs, the public has been promised real benefits within 5–10 years (i.e., in this case, significant stem cell therapies in routine clinical use). Several of the 5–10 years have now elapsed, and the promised therapies are still not anywhere close to routine clinical use.[6]

A typical example of this kind of argumentation is found in the document of opinion, "Ethical aspects of human stem cell research and use," of the European Commission's Group on Ethics in Science and New Technologies:

> The Group notes that in some countries embryo research is forbidden. But when this research is allowed, with the purpose of improving treatment of infertility, *it is hard to see any specific argument which would prohibit extending the scope of such research* in order to develop new treatments to cure severe diseases or injuries. As in the case of research on infertility, stem cell research aims to alleviate severe human suffering.[7]

In their account, the Group seems to take for granted not only that the motivation behind embryonic stem cell research is of the same alleviating kind as embryonic research to improve treatment of infertility but also that the current situation of estimating the benefits of embryonic stem cell research is comparable to the situation at the time when embryonic research aimed at improving treatment of infertility was introduced by the end of the 1970s. Such a comparison is, however, hardly warranted. At the time when embryonic research to improve treatment of fertility was introduced, IVF was already an existing form of treatment, albeit with a lower success rate than quantifiable estimates suggested that it was possible to achieve by allowing methodological research on human embryos. Embryonic stem cell research, on the other hand, is still in an "embryonic state," to use Holm's expression, still far away from any possibility of quantifying its therapeutic potentials. Or, to put it more bluntly: The empirical basis for using the "beneficial" sacrifice of human embryos involved in research aimed at infertility treatment as a justification for extending the scope of destructive research to include embryonic stem cell research is simply nonexistent. Consequently, the Group's inference from analogy also has to be rejected.

Fact-Finding Narratives

Although there are numerous other examples in the literature of similar attempts at therapeutically overselling embryonic stem cell research,[8] this does not represent the whole story. Alternative "scientific" narratives are repre-

sented in the debate as well and deserve more moral attention than hitherto given. One of the most recent of such accounts is to be found in the report on stem cell research issued by the House of Lords Select Committee, mentioned previously. What makes this report a different reading from many other contributions is that priority is given to identifying various forms of *basic* stem cell research that need to be undertaken *before* anything can be said definitely about the possibilities of performing preclinical studies or large-scale clinical trials. No attempt is made here at "promising too much too early," to use again Holm's formulation. On the contrary, the authors of the report are cautious to get the vital facts as straight as possible and to bring speculations down to a minimum:

> The great majority of potential stem cell-based therapies are still at the first stage of this process, basic scientific research.[9]
>
> From the evidence we have received we are clear that over the next few years most studies on stem cells, whether adult, foetal or embryonic in origin, will be basic research. This research will not in itself be therapeutic, but will be undertaken with the aim of gaining the understanding necessary if stem cells are to be used widely for therapeutic benefit.[10]

In the Select Committee's report, nine basic research challenges are identified as necessary to explore, prior to attempts at performing preclinical or clinical studies on living individuals:

1. identification and characterization of stem cell specificity
2. isolation and purification of specific stem cells in "sufficient number to be useful"
3. creation of *clean* growing conditions in vitro
4. maintenance of stability of acquired properties after manipulation
5. directed stem cell differentiation
6. controlled stem cell integration
7. proper understanding of the processes of de- and redifferentiation
8. control of stem cell migration
9. avoidance of immunological rejections.

Competing Stories of Redundant Research

In its response to the question whether research on human embryonic stem cells is *necessary* to cope with these challenges, the Committee relies on a set of empirical premises worth closer examination. The first premise is that studies suggesting a higher degree of plasticity among certain types of adult stem cells "are still open to multiple interpretations or require replication."[11] The confused debate evoked by the publication of two recent studies in *Nature*—notably published only in the form of *letters*—on spontaneous fusion of stem cells confirms the soundness of this precaution.[12] The authors behind the letters do not—as reported by several news agencies and reiterated in *Nature Biotechnology* and the *British Medical Journal*[13]—call into question the possibility of a higher plasticity in adult stem cells than previously believed, nor do they deny the existence in vivo of the phenomenon of *proper* transdifferentiation in such

cells. Instead, they draw attention to the phenomenon of spontaneous fusion taking place in vitro between embryonic stem cells and adult stem cells and suggest that differentiation properties in adult stem cells may be explained along this alternative pathway. As admitted by the group of researchers behind one of the letters, whether and to what extent cell fusion contributes to the formation of "apparently transdifferentiated cells in vivo is currently pure speculation; however," the letter continues, "our data raise a warning to the overzealous trend in stem cell research to conclude transdifferentiation or dedifferentiation of cells without careful examination of genotypes."[14]

In a subsequent Commentary in *Nature Biotechnology* to these studies,[15] Ron McKay writes that, although there are other studies indicating that cell fusion is not necessary for transdifferentiation to take place,[16] experiments that "directly show that stem cells are changing their fate" would still be needed to settle the question. And in a second Commentary on somatic stem cell plasticity published in the same issue of *Nature Biotechnology*, Ihor Lemischka pinpoints quite eloquently the current lack of experimental clarity on the issue of somatic stem cell plasticity:

> Recently, several publications have appeared that highlight the sometimes unexpected complications that can arise in studies of stem cell plasticity.[17] In short, these studies support the notion that extraordinary claims will require an extraordinary degree of experimental rigor.[18]

The second empirical premise on which the House of Lords Select Committee relies is oral and written evidence from a wide range of individuals (experts and lay people) and professional organizations. The result of these consultations was that very few experts—notably none of the consulted experts on *adult* stem cells![19]—supported the view that the recent developments on adult stem cells had made embryonic stem cell research redundant. Positively formulated, the message conveyed to the Committee was that, in the present situation of substantial ignorance about what represents the best route, adult stem cells and embryonic stem cells should not be viewed as research *alternatives* but as "complementary pathways to therapy."[20]

A third empirical premise relates to the processes of de- and redifferentiation, which it would, according to the Committee, be unrealistic to understand thoroughly without using pluripotent stem cells that are fully undifferentiated (i.e., embryonic stem cells). Although most of these studies can be undertaken on embryonic stem cells derived from *animals*, the Committee states that comparison with human embryonic stem cells would be required prior to attempts at applying the results to develop therapies. Consequently, it seems that a certain amount of basic research on human embryonic stem cells would still be necessary.

To further substantiate this point, the Committee also points to the complications involved in using adult stem cells instead to study the mechanisms underlying these processes:

> If scientists are to dedifferentiate adult stem cells to pluripotency, prior to redifferentiation into a new cell type for therapeutic purposes, they must know whether they have done this correctly and whether the process is safe. Differentiation involves "marking" the genetic material

> in a number of ways. These "markings" (including chemical changes to the DNA and the interaction of specific proteins with it) are "remembered" during cell division. If an adult stem cell is to be dedifferentiated prior to redifferentiation for therapeutic purposes, these markings must be correctly erased.[21]

A final premise underlying the Committee's rejection of the redundancy argument against human embryonic stem cell research is that, although it may be probable that future developments will make research on human embryonic stem cells unnecessary, the present lack of any reliable predictions about which route represents the best option "suggests that avenues of research should not be closed off prematurely."[22]

To complicate the issue of prediction a bit further, suffice it here to refer to a newly published study in which an in vitro method for analyzing the mechanisms underlying nuclear reprogramming is presented and where it is suggested that differentiated somatic cells may not only be used to investigate the mechanisms underlying the processes of de-, re-, and transdifferentiation but also to produce "isogenic replacement cells for therapeutic applications."[23] If this prediction comes true, then it may very well be that a third route to cell therapy will also see the day. However, as pointed out by Western and Surani:

> The applicability of this technology in producing reprogrammed cell lines for therapeutic purposes remains undetermined. A large amount of additional data are required before such a system could be applied to the generation of stem cells to be used directly in cell replacement therapies for human patients.[24]

To sum up the analysis so far: In its attempt at scientifically defending the case of embryonic stem cell research, the House of Lords Select Committee makes use of a combined strategy of

1. identifying a set of *basic* research challenges that need to be addressed prior to any attempts at therapeutic research applications, and
2. paying particular attention to recent developments in *adult* stem cell research.

Although hailing the therapeutic potential of adult stem cell research as "great," the Committee concludes that in the meantime human embryonic stem cell research remains a "clear" and "strong" case, scientifically as well as medically.[25] This way of resolving the story of redundancy stands in contrast to Søren Holm's challenging account, where the available scientific evidence is not found to be strong enough to warrant human embryonic stem cell research. According to Holm, as long as the scientific evidence available does not demonstrate with unequivocal certainty that human embryonic research is *necessary*, stem cell research should be restricted to nondestructive lines of research.[26] Holm bases his negative verdict on two empirical premises: The lack of *compelling* evidence to suggest that

1. human embryonic stem cell research will bring about therapeutic results "much faster" than adult stem cell research, or

2. that human embryonic stem cell research represents the only available pathway to generate cures for certain diseases.[27]

By restricting himself to these two "therapeutic" premises, Holm manages to build up a seemingly convincing case against destructive stem cell research on human embryos. The problem, however, is that there is one part of the story that is missing in his account: the part that, at least for the time being, represents the main chapter—*basic* scientific research. Holm rightly draws attention to a tendency among proponents of embryonic stem cell research of therapeutically *overselling* their case. However, by leaving out the premise of basic research in his *own* account, Holm risks ending up *rejecting too much too quickly* and notably by employing the same contestable strategy as the enthusiasts of human embryonic stem cell research: the overselling—or perhaps a more appropriate wording in this case would be, the "over-killing"—of *therapeutic* arguments! A preliminary conclusion that might be drawn from this analysis therefore is that, at present, the use of *therapeutic* arguments, either to justify human embryonic stem cell research or to contest such research, should be rejected as *overuse*—if not necessarily as *abuse*—of scientifically available evidence. On the other hand, further analysis is needed to clarify whether the House of Lords Select Committee is justified in claiming that at least some of the *basic* research challenges identified in the report cannot be adequately explored without allowing the use of—spare or created—human embryos.

Different Stories of Differentiation

This brings me back to the third empirical premise in the Select Committee's defense of human embryonic stem cell research: the need to understand and technically cope with the different processes of cell differentiation (research challenges 5 and 7 identified in the House of Lords' report). As stated by the Committee, in the first place, only research on embryonic stem cells derived from *animals* needs to be carried out. However, to be able to translate those results into something that can be used to develop therapies in the *human* sphere, similar studies on human embryonic stem cells to confirm—and eventually adjust—the results will also be necessary. Thus, the Committee argues, research into human embryonic stem cells is required whatever cell type (embryonic or adult stem cells) will be used in the future for therapeutic purposes, as "apart from CNR, ES cells provide the only realistic means at present of studying the mechanisms and control of the processes of differentiation and dedifferentiation."[28]

It might however be that this is no longer the case, if we take into account the newly published study of an in vitro method using differentiated somatic cells for investigating the mechanisms underlying these processes, but further research would be needed before the true potential of this method is clearly demonstrated. Besides, in case this method really proves to be efficient in deciphering the different processes of cell differentiation, human embryonic stem cells would probably still be required as "control cells" to verify whether adult stem cells are really undergoing *complete* and *proper* dedifferentiation. Consequently, a certain amount of basic research on human embryonic stem cells seems to be unavoidable. A second argument in favor of including embryonic stem cells in the study of the processes of de- and redifferentiation is that, the sooner one

gets a clear understanding of these processes, the sooner will it also be possible to start researching the therapeutic potential of *adult* stem cells. Thus, by including embryonic stem cells as proper objects of study to understand the processes of de- and redifferentiation, there are strong reasons to believe that valuable scientific results would be produced much faster than if basic research is confined to adult stem cells.

Competing Stories of Embryonic Origin

A remaining set of empirical premises that needs to be addressed relates to the question of embryonic *origin*—that is, to the question of which type of embryo would be preferable to use if human embryonic stem cell research is deemed necessary. In its report the Select Committee suggests that *surplus* embryos from IVF treatment should be the *first* choice, whereas the intentional creation for research purposes of human embryos by IVF should not be allowed "unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos."[29] Two empirical premises are in operation behind the Committee's assessment: the huge amount of surplus IVF human embryos having been donated for IVF-related research (53,497) and the small number of additional IVF embryos having been found necessary to create for that specific purpose (118) in the period between 1 August 1990 (when the Human Fertilisation and Embryology Act came into force) and 31 March 1999.[30] As for the possibility of using CNR technology to produce embryos for research, the Committee argues from the premise that CNR represents a *powerful* research tool to understand the mechanisms underlying the processes of de- and redifferentiation. However, in spite of its positive verdict, the Committee suggests that production of CNR embryos should be restricted in the same way as is the creation of research embryos by IVF, to minimize the risk of *instrumentalization* of human life to a degree beyond that of a research practice restricted to the use of surplus IVF embryos.[31] Finally, the Committee refers to the "excellent record" of the Human Fertilisation and Embryology Authority as convincing evidence for the possibility of monitoring embryonic research in a way sufficient to protect against any unwarranted practice of embryonic research, reproductive cloning included.[32]

Concluding Remarks about an Unfinished Story

The devil is in the details. This well-known remark seems appropriate to sum up the results of the stem cell controversy so far. As the above analysis has shown, the abundant use of *therapeutic* arguments to justify human embryonic stem cell research lacks empirical foundation. It represents unwarranted exploitation of scientifically available evidence. This negative conclusion also seems to hold true for the opposite case—that is, of using therapeutic arguments to question the necessity of human embryonic stem cell research. Although failing to get all the details right does not necessarily mean that the overall story will end up distorted, in the case of stem cell research it seems justified to say that empirical details deserve more attention in the ethical debate than hitherto given. Consequently, the empirical case in favor of a limited amount of destructive *basic* research on human embryos should also be included in the account. As to the question of embryonic origin, the huge amount of surplus

embryos from IVF supports their selection as *primary* source for basic stem cell research. On the other hand, available evidence also suggests that the use of CNR, and thereby the production of human embryos, might become necessary to understand the mechanisms underlying the processes of de- and redifferentiation. Third, there is little evidence available to support the view that creation of IVF embryos for stem cell research is necessary. Finally, the recent publication of a study reporting the discovery of a previously unknown type of cells in *adult* bone marrow—so-called multipotent adult progenitor cells—with an in vitro ability of differentiation comparable to human embryonic stem cells and with the capacity of organ-directed differentiation in vivo,[33] makes clear that this is an ever-evolving narrative.

Notes

1. Holm S. The ethical case against stem cell research. *Cambridge Quarterly of Healthcare Ethics* 2003, this issue, 372–83.
2. Holm S. Going to the roots of the stem cell controversy. *Bioethics*, 2002;16(6):493–507.
3. See note 1, Holm 2003:372–83.
4. See note 2, Holm 2002:494.
5. House of Lords. *Stem Cell Research: Report from The Select Committee*. 2002 Feb 13:2.12.
6. See note 1, Holm 2003:374. See also note 2, Holm 2002:502.
7. European Group on Ethics in Science and New Technologies to the European Commission. *Ethical Aspects of Human Stem Cell Research and Use*. 2000 Nov 14:2.5.
8. See, for example: Hansen JES. Embryonic stem cell production through therapeutic cloning has fewer ethical problems than stem cell harvest from surplus IVF embryos. *Journal of Medical Ethics* 2002;28:86–8.
9. See note 5, House of Lords 2002:2.11.
10. See note 5, House of Lords 2002:2.12.
11. See note 5, House of Lords 2002:3.15.
12. Terada N, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y et al. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* 2002;416:542–5; and Ying QL, Nichols J, Evans EP, Smith AG. Changing potency by spontaneous fusion. *Nature* 2002;416:545–8.
13. For this, see, for example: Flaws in studies of adult stem cells dash medical hopes. *Daily Telegraph* 2002 Mar 14; Study weakens anti-abortionists' adult tissue claim. *The Independent* 2002 Mar 14; Experts question studies suggesting adult stem cells won't work. *CNSNews.com* 2002 Mar 15; Turning back the clock. *Nature Biotechnology* 2002 May 20:411: "The finding that ES cells can fuse with adult stem cells in coculture throws into question whether previous observations of transdifferentiation were due to reversion of adult stem cells or expansion of abnormal hybrids"; Mayor S. Adult stem cells may not be able to differentiate into other cell types: news roundup *BMJ* 2002;324:696. See also: Researcher says media distorted adult stem cell studies. *CNSNews.com* 2002 Mar 25, where, Dr. Naohiro Terada, one of the researchers behind one of the studies on cell fusion is quoted saying, "Our message was somehow distorted by the media" and "We never said adult stem cells are no longer hopeful, nor dangerous. If someone took our message that way, that is a misinterpretation."
14. See note 11, Terada, Hamazaki, Oka, Hoki, Mastalerz, Nakano et al. 2002:544.
15. McKay R. A more astonishing hypothesis. *Nature Biotechnology* 2002;20:426.
16. McKay's reference is to the following studies: Rolink AG, Nutt SL, Melchers F, Busslinger M. Long-term in vivo reconstitution of T-cell development by Pax5-deficient B-cell progenitors. *Nature* 1999;401:603–6; Seale P, Sabourin LA, Girgis-Gabardo A, Mansouri A, Gruss P, Rudnicki MA. Pax7 is required for the specification of myogenic satellite cells. *Cell* 2000;102:777–86; McKinney-Freeman SL, Jackson KA, Camargo FD, Ferrari G, Mavillio F, Goodell MA. Muscle-derived hematopoietic stem cells are hematopoietic in origin. *Proceedings of the National Academy of Sciences USA* 2002;99:1341–6.
17. In addition to the two studies on cell fusion already referred to (see note 11, Terada et al. 2002; see note 16, McKinney-Freeman et al. 2002), Lemischka also mentions the following study:

Morshead CM, Beveniste P, Iscove NN, van Der Kooy D. Hematopoietic competence is a rare property of neural stem cells that may depend on genetic and epigenetic alterations. *Nature Medicine* 2002;8:268–73.
18. Lemischka I. Rethinking somatic stem cell plasticity. *Nature Biotechnology* 2002;20:425.
19. The Committee received replies from four internationally renowned experts on adult stem cells: Professor Helen Blau, Stanford University School of Medicine; Dr. Jonas Frisen, Karolinska Institute, Stockholm; Professor Nadia Rosenthal, The European Molecular Biology Laboratory, Monterotondo-Scalo, Italy; and Professor and Director Angelo Vescovi, The Stem Cell Research Institute, Milan.
20. See note 5, House of Lords 2002:3.16.
21. See note 5, House of Lords 2002:3.18.
22. See note 5, House of Lords 2002:3.19–21.
23. Håkelien AM, Landsverk HB, Robi, JM, Skålhegg BS, Collas P. Reprogramming fibroblasts to express T-cell functions using cell extracts. *Nature Biotechnology* 2002;20:460–6.
24. Western PS, Surani MA. Nuclear reprogramming—alchemy or analysis? A new strategy for nuclear reprogramming using cell extracts induces fibroblasts to express hematopoietic and neuronal responses. *Nature Biotechnology* May 2002;20:445–6.
25. See note 5, House of Lords 2002:3.22ff. For the wording, see also the report's Summary of Conclusions and Recommendations, paragraph 4.
26. See note 2, Holm 2002:505–6. See also note 1, Holm 2003.
27. See note 1, Holm 2003.
28. See note 5, House of Lords 2002:3.17.
29. See note 5, House of Lords 2002:4.28.
30. See note 5, House of Lords *Report* 2002:4.26. Reference is made to the *Human Fertilisation and Embryology Authority* (HFEA), Ninth Annual Report and Accounts, 2000.
31. See note 5, House of Lords 2002:5.14.
32. See note 5, House of Lords 2002:5.24.
33. Jiang Y, Balkrishna N, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR et al. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* [advance online publication] 2002 Jun 20. Available at: http://www.nature.com, doi:10.1038/nature00870.