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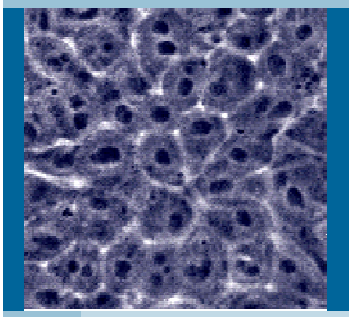

CANADIAN CATHOLIC BIOETHICS INSTITUTE

Bioethics Update

Human Embryonic Stem Cell Research: Unsettled Questions

In a letter to the U.S. Congress in 1999, thirty-three Nobel laureates wrote, "Those who seek to prevent medical advances using stem cells must be held accountable to those who suffer from horrible disease and their families, why such hope should be withheld ."[1] These strong words articulate the sentiments of many scientists and a segment of the public, but they appear to place the burden of proof on the wrong shoulders.

Making responsible judgements in bioethics demands that we do not hasten to act without first having settled, to the extent possible, important factual or moral questions relevant to a clinical or research situation. If we are compelled to do so because there is some urgency to decide, it is always with moral disquiet and regret. Understanding bioethical inquiry in this way suggests a different approach to the issue of human embryonic stem cell research than the one expressed by the Nobel laureates. Those who seek the freedom and public funding to experiment with human embryonic stem cells must show that there are no relevant questions about such research that it would be *irresponsible* for society to leave unsettled. The aim of this review is to propose that the factual and moral uncertainties of using human embryonic stem cells for research are serious enough to warrant caution despite the promise of greatly desired future benefits.

Definitions

Let us first be clear about some definitions. The Working Group on Stem Cells of the Canadian Institutes of Health Research (CIHR) defines stem cells as cells that "have the unique property of being able to either reproduce themselves (a process called "self-renewal") or differentiate into a variety of more specialized cells."[2]

The terms "totipotent","pluripotent" and "monopotent" are commonly applied to stem cells. Totipotent cells are capable of becoming any cell; pluripotent cells, to varying degrees, are able to change into many but not all cell types; multipotent cells can regenerate cells only of a very limited variety. It is important to realize that these distinctions may reflect limitations in our scientific knowledge rather than any real distinction in cells. As we discuss below, there are very rapid changes in our current understanding of how cells change. We may discover that cells are more adaptable than we think. We cannot at present rule out the possibility that any type of cell in the body can be reprogrammed to become any other type.[3] If this is the case, our classification of what cells are "stem cells" and which are "pluripotent" as opposed to "multipotent" are all open to future revision. Moreover our reliance on embryonic stem cells will be diminished.

(continued on p.2)

Human Embryonic Stem Cell Research —– continued

Sources of Stem Cells and the Canadian law

The definitions above, although open to future revision, have been used to rank the usefulness of various sources of stem cells for research into new treatments.[4] Currently there are several sources for stem cells: embryos, cells from the gonadal region of fetuses aborted for reasons other than research[5], blood cells from the placenta and umbilical cord of babies[6], about 20 different kinds of adult body cells as of July 2000[7].

Scientists often claim that embryonic stem cells are more beneficial to use for research into new treatments than stem cells from other sources. Embryonic stem cells may be obtained from (1) embryos created by *in vitro* fertilization that are designated as "surplus"; (2) embryos that are created *in vitro* from human sperm and egg donated specifically for research; (3) embryos created by an asexual cloning technique called "somatic cell nuclear transfer". Here the genetic material of any body cell is put into an unfertilized human egg with its own genetic material removed. When further development of the embryo is stopped to obtain stem cells for research into treatments, this process is called, euphemistically, "therapeutic cloning"; (4) hybrid embryos (chimeras) created by transfer of human genetic material into an animal egg; (5) cell lines derived from the reproduction of embryonic stem cells obtained originally through the first four means.

Draft legislation introduced by the Canadian federal government on May 3, 2001 permits the controlled use of stem cells from surplus *in vitro* embryos up to 14 days after fertilization, provided that researchers have informed consent from donors who are not reimbursed and a Health Canada licence. The proposed law prohibits creating embryos *in vitro* from sperm and eggs donated or purchased for research or from asexual cloning. It does not forbid, but only regulates by licence, the creation of chimeras.

Compared to British law, which allows the creation of embryos for research by asexual cloning, there is a great deal of merit to the Canadian draft legislation. Compared to American policy, which allows public funding of research derived only from existing stem cell lines, the Canadian draft legislation and the CIHR discussion paper envision law and policies that are more permissive.

There is a general perception that the Canadian position is the best of the three simply because it is *intermediate*. This often slips into the claim that Canadians have the best possible *ethical* position given the diversity of opinions on the use of human embryonic stem cells. Such a claim confuses ethics with politics. Ethics does not take as a given that the middle ground on contentious issues is always the best.

The proposed Canadian legislation sidesteps some scientific, philosophical and social questions that pertain to *what* a human embryo is prior to14 days of development and whether such embryos created *in vitro* have a claim on society's protection. These questions will be discussed in detail in a paper being written by researchers of the Canadian Catholic Bioethics Institute. For now it is sufficient to highlight briefly what some of these important questions are.

Scientific Questions

There is no dispute among scientists that what results from the fertilization of a human egg and sperm is human life. One unsettled question is when the resulting embryo can be observed to be an *individual* human life. (This is different from the philosophical question of individuality discussed below.) The 14-day criterion used in proposed Canadian legislation as the cut-off point for destroying *in vitro* embryos is based partly on *currently accepted estimates* of when the process of twinning (generating separate individuals from the same embryo) stops. The unstated presupposition seems to be that the sacrifice of

as few potentially viable embryos as possible is to be desired. It is important to realize both that the 14-day criterion is open to revision and that it is an upper-limit without a corresponding lower-limit. The significance of the second point is that a common practice in *in vitro* fertilization clinics is to freeze (cryopreserve) embryos in the 4-8-cell stage of embryonic growth. Each of these is thought to be still totipotent and capable of growing into separate living embryos.[8] These scientific distinctions might be pointless if it is presumed that excess embryos in fertility interventions will be discarded any way if not used for research. Society should not take it as a given, however, that there are only two possible fates for such embryos. Adoption is an alternative.

The broader scientific question that remains unresolved is whether there are sufficient empirical grounds for believing that human embryonic stem cell research will generate new treatments that stem cells from other, less morally problematic, sources cannot. Before the promise of therapeutic benefit can be realized, scientists need to understand: (1) how to grow large-scale cultures of stem cells and at the same time arrest their development; (2) how to direct change of embryonic stem cells into a specific kind of cell; (3) how to isolate and maintain pure cultures of differentiated cells in order to avoid tumour formation; (4) how to ensure that these cells are functional in tissues after transplantation; (5) how to prevent rejection of transplants by hosts.[9] The irony is that, when we arrive at the necessary understanding and technical skills to overcome these barriers in embryonic stem cells, we would have fewer reasons not to use adult stem cells. Already research with adult stems cells has exceeded scientists' expectations in terms of ease of growth and versatility, at least in animal models, with an advantage over embryonic stem cells in terms of immunological acceptance by transplant recipients.10 It is true that thereotically it might be easier to direct the development of an unspecialized embryonic stem cell than to reprogramme an already differentiated adult cell. Nevertheless there is no direct evidence yet of a significant difference.

Philosophical Questions

Different from empirical questions of the sort outlined above are philosophical questions about the moral status of the early embryo. The key question is whether and when to attribute "personhood" and thus moral value to the early human embryo prior to 14 days of growth. There are at least three distinct positions: that the early embryo has no moral value because it is essentially a clump of undifferentiated cells; that the early embryo has some moral value by virtue of its being a "potential person", but this is not equivalent to the moral value of children and adults; that it is an actual person and thus merits protection of its existence and continued development.

The issue of personhood is often viewed as an insurmountable stumbling block in public debates on human embryonic stem cell research because the battle lines, so to speak, are so clearly drawn. On an issue such as this, opponents may lock horns on at least three levels: There may be disputes about specific positions on the issue, about the sufficiency of evidence put forward in support of those positions, and about *what sort of evidence should count* in the debate. On the moral status of the early embryo, most of the literature focuses on disputes on the first two levels outlined above. The third level involves often unstated philosophical presuppositions about criteria for valid human knowing. The discussion paper currently being written by the Canadian Catholic Bioethics Institute attempts, in part, to bring to light some of these fundamental presuppositions and to compare them in terms of adequacy.

Briefly the paper shows that those who claim that the early embryo is an actual person ground their claim on an insight that the observed bunch of

undifferentiated cells prior to 14 days after fertilization already has a unity that is the cause of why further cell divisions and differentiations occur in a specific orderly way, provided that there is no natural or artificial interference. Even though not all the parts of this unity have fully emerged, the embryo will grow these parts on its own and in a systematic way. Without a 'whole being' present from the start, further growth and origination of parts in the early embryo could never take place in a way that is orderly and geared towards a specific biological end. This insight is based on the ability to understand a certain dynamic pattern of development in the empirical data. Its basis, therefore, is both empirical and intelligible. By contrast, the paper shows that those who argue that the early embryo is not a person or only a potential person rely on evidence that is either only empirical or only intelligible.

Social Questions

NOTES

1. Letter to Congress and President Clinton, March 4, 1999. Quoted in Andrew W. Siegel, "Neutrality and consensus: towards a viable policy on human stem cell research", *Molecular Aspects of Medicine* 22 (2001): 171-181, on p. 171.
2. Canadian Institutes of Health Research, *Human Stem Cell Research: Opportunities for Health and Ethical Perspectives. A Discussion Paper*. Ottawa: CIHR, 2001, p. 1.
3. Ferdinand Hucho, "Stem cells: An introduction to the biology of an unclear promise", *Molecular Aspects of Medicine* 22 (2001): 143-147, see p. 145.
4. The qualifier "into new treatments" is significant here because scientists have proposed other benefits of using embryonic stem cells. See Martin F. Pera, Benjamin Reubinoff, Alan Trounson, "Human embryonic stem cells", *Journal of Cell Science* 113 (2000): 5-10, esp. p. 5.
5. M. Shamblott *et al*., "Derivation of pluripotent stem cells from cultured human primordial germ cells", *PNAS* 95 (1998): 13 726-13 731.
6. There are ethical issues concerning umbilical cord blood banking that this paper will not address but are summarized in Ronald M. Kline, "Whose blood is it, anyway?", Scientific American 284 (April 2001): 42-49.
7. Hucho (n. 3), p. 145.
8. It is thought that once the embryo has developed an outer layer (trophectoderm), stem cells harvested from the inner cell mass of an embryo can no longer develop the placenta that is needed for nutrition and protection. This differentiation occurs by at least the 32-cell or blastocyst stage of the embryo. In the last year, scientists have identified a genetic factor (oct-4) that plays a key role in causing the cells of the inner cell mass to differentiate into cells of the trophectoderm. See M. Pesce and H.R. Scholer, "Oct-4: gatekeeper in the beginnings of mammalian development", *Stem Cells* 19 (2001): 271-8.
9. Beverly Purnell, "Bioetchnology: Large-Scale Growth", *Science* 294 (Nov. 9, 2001): 1243; Anna M. Wobus, "Potential of embryonic stem cells", *Molecular Aspects of Medicine* 22 (2001): 149-164, esp. pp. 157-8; Pera (n. 4), 9.
10. See for example, Eva Mezey et al., "Turning blood into brain: Cells bearing neuronal antigens generated in vivo from bone marrow", *Science* 290 (Dec. 1, 2000): 1779-1782.