Inconsistencies in Pro ANT-OAR Position

In the January 30, 2006, issue of the *National Catholic Register*, a Catholic weekly newspaper, Rev. Thomas Berg, LC, of the Westchester Institute in Thornwood, New York, wrote an opinion piece titled "Cloning, After Hwang" that is, unfortunately, riddled with inconsistencies.[1]

In his essay, Fr. Berg uses the recent discovery of data fabrication by South Korean cloning researcher Woo-Suk Hwang as a springboard to raise concerns about a possible redoubling of efforts by American scientists to get so-called therapeutic cloning to work and to pass federal legislation allowing the use of "surplus" embryos from in vitro fertilization (IVF) for obtaining stem cells. He argues that pro-cloning and pro-embryonic-stem-cell-research advocates have a political agenda, that of "breaking down public and Congressional resistance to using left-over embryos," because doing so "is a crucial step toward garnering public acceptance of the creation (and destruction) of new embryos for research." He also laudably advocates for adult stem cell research.

So far, so good. The problems start when Fr. Berg puts forth an argument in favor of so-called alternative methods for deriving stem cells, including a completely speculative procedure known as altered nuclear transfer–oocyte assisted reprogramming (ANT-OAR). The claim Fr. Berg makes in support of ANT-OAR is that the entity produced by the procedure would not be a bona fide embryo, but instead would be a pluripotent stem cell. Thus, ANT-OAR claims to directly produce a stem cell, effectively bypassing the embryo stage altogether.

As it turns out, Fr. Berg was one of the original architects of the ANT-OAR proposal, having convened a meeting in April 2005 that led to its formal adoption by a group of thirty-five, mostly Catholic moral theologians, ethicists, and scientists.[2]

Just what are the inconsistencies in Fr. Berg's essay, then? There are several. First, although he criticizes cloning advocates, ANT-OAR itself is a type of human cloning, also known as somatic cell nuclear transfer (SCNT). The only difference is that, with ANT-OAR, the somatic cell nucleus is genetically altered prior to transfer in order—

This essay was originally submitted, in shortened form, as a letter to the editor of the *National Catholic Register*. However, the newspaper declined to publish it.

[1] *National Catholic Register*, January 29–February 4, 2006, http://www.ncregister.com/articulo2.php?artkod=MTc4.

[2] See "Production of Pluripotent Stem Cells by Oocyte-Assisted Reprogramming: Joint Statement with Signatories," *National Catholic Bioethics Quarterly* 5.3 (Autumn 2005): 579–583.

so proponents claim—to produce a stem cell without producing an embryo. The problem, however, is that, ANT-OAR advocates' arguments notwithstanding, there is no firm basis for believing this claim. As a biochemist and molecular biologist, I—along with a number of other scientists and physicians in different fields[3]—entertain serious doubts that ANT-OAR could ever work scientifically. Why? In a nutshell, the genetic or biochemical alteration it introduces, which causes over-expression of a protein called NANOG, would take effect outside the delicate developmental context in which NANOG normally operates. In fact, based on the science, the most likely result of ANT-OAR would be, instead of a pluripotent stem cell, either a dead embryo or a disabled one that hobbles along defectively. It is ironic, indeed, that Berg criticizes scientists' efforts to get SCNT to work in humans when the procedural centerpiece of ANT-OAR is SCNT. One would expect Fr. Berg to hang his head in disappointment in response to the news that Hwang's apparent cloning successes were the result of fraud. Instead, he inconsistently calls for a federal ban on human SCNT, even though it is the key to the success of the "alternative" he is proposing.

Second, Berg accuses advocates of embryonic stem cell research and cloning of adopting the mantra "if it can't implant, it's not human." But ANT-OAR follows a similar rationale, which is "if it can't develop properly or beyond a certain point, it's not human." The only difference between ANT-OAR and the use of stem cells from IVF embryos is that the decision not to allow the embryo to develop further is made *in advance* in the case of ANT-OAR, by genetically engineering the somatic cell nucleus before it is transferred in the cloning step and/or by injecting *Nanog* messenger RNA into the enucleated oocyte before transfer. Moreover, one could legitimately argue, ANT-OAR is actually *worse* than embryonic stem cell research. Why? Because ANT-OAR, whether advocates realize it or not, involves the actual creation of genetically engineered human embryos (albeit defective ones) for medical purposes. If there ever were a slippery slope into a brave new world, this is one.

Third and finally, Fr. Berg accuses advocates of cloning and embryonic stem cell research of having a political motive: to break down the social barriers to using leftover IVF embryos for research. But Berg himself clearly has a political motive as well. ANT-OAR was proposed partly to give President George Bush, who is perceived as being pro-life, political cover. If Bush were simply to veto a Congressional bill allowing leftover IVF embryos to be used for research, he would appear anti-science to many Americans, two-thirds of whom favor embryonic stem cell research. But if he could sign a bill allowing an "alternative," non-embryo-destructive method for deriving embryonic stem cells, then he would win on both counts. He would be seen as both pro-science and pro-life. Thus, although Fr. Berg accuses cloning and embryonic stem cell proponents of having a shrewd political agenda, it is clear that he has one, too.

OAR not only has no solid basis in scientific fact, then, but was conceived in a politically charged atmosphere. Yet, while it is one thing to play politics with science, it quite another thing to play around with the beginnings of human life. No political gain, however alluring, is worth the erosion of the respect for human life that would result.

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[3] See W. J. Burke, P. Pullicino,and E. J. Richard, "Stemming the Tide of Cloning," *First Things* 158 (December 2005): 6–8. For critiques of the feasibility of ANT, from which OAR is derived, see D. A. Melton, G. Q. Daley, and G.. C. Jennings, "Altered Nuclear Transfer—A Flawed Proposal," *New England Journal of Medicine* 351.27 (December 30, 2004): 2791–2792; and D. Solter, "Politically Correct Human Embryonic Stem Cells?" *New England Journal of Medicine* 353.22 (December 1, 2005): 2321–2323.

Fr. Berg replies:

Malcolm Byrnes has raised concerns about my support for ANT-OAR, and the editors of the *Quarterly* have asked me to respond. I salute the very evident pro-life convictions that animate Byrnes' response to my original article in the *National Catholic Register.* However, I think his critique is off the mark in several respects.

First, there is no inconsistency in advocating research into ANT-type experiments on the one hand, and opposing human *cloning* on the other. *Cloning* is normally understood to mean the asexual production of a living *organism*, virtually genetically identical to the organism from whose cells the cloned organism originated. When pursued in plants and nonhuman animals, most agree that cloning for legitimate purposes is morally uncontroversial. The cloning technique is per se wrong only if it is used to make a human embryo—a living organism of the human species at the earliest stage of development.

If the cloning technique could be altered to produce "pluripotent" (embryonic-like) stem cells *without* making an embryo, this would clearly serve medical research without violating human dignity. In my *Register* article, I pointed out that ANT-OAR indeed proposes to use the cloning technique (nuclear transfer), but precisely with this very different end in view, namely, the production of a culture of pluripotent stem cells, not an embryo.

Specifically, as Byrnes himself points out, ANT-OAR seeks to change the factors that guide gene expression before the nucleus of a body cell is joined to an enucleated egg. *If* the technique works as planned (and that is a big *if*, requiring further investigation—a point often lost on some critics of ANT), the resulting product would have the gene expression pattern (hence the developmental trajectory) of a stem cell, and *not* that of an embryonic human organism, *from the very beginning*. ANT-OAR, as one possible variation of the broader ANT conceptual proposal, does *not* seek to make a damaged, short-lived, or booby-trapped embryo. Rather, it proposes to produce something that from the outset *is not a human organism at all*.

Because ANT-type approaches would be gravely unethical if they did create embryos—healthy, disabled, or otherwise—they must be thoroughly tested using animal cells before anyone could responsibly pursue them using human cells. At present, the only thing that supporters of ANT-type solutions are endorsing is further examination using these approaches in animal models. I fail to see why such experiments should raise moral concerns.

Second, contrary to Byrnes' assertion, ANT-OAR (or ANT-type experiments more broadly) would *not* run afoul of proposed anti-cloning legislation. The most salient anti-cloning bill currently on the table is S. 658, the federal Human Cloning Prohibition Act, passed by the U.S. House of Representatives and introduced in the Senate by Senator Sam Brownback (R-KS). The Brownback bill would ban the use of the nuclear transfer technique to create a human embryo, a living organism of the human species. However, it explicitly permits the use of any cloning technique "to produce molecules, DNA, *cells other than human embryos*, tissues, organs, plants, or animals other than humans." ANT-type approaches would clearly be permissible under such a law. That is why last February, I, along with many of the original ANT-OAR supporters, publicly expressed our support for the effort to pass this law.[1] We see it as entirely consistent with, and complementary to, responsible efforts to explore ANT.

Third, Byrnes suggests that I have been less than forthcoming about my "political" motives for supporting ANT-OAR. I will give Byrnes the benefit of the doubt that he is not calling into question my pro-life convictions or those of the other thirty-four signatories of the original ANT-OAR proposal. That proposal was conceived, like other alternatives

[1]See "Human Cloning and 'Altered Nuclear Transfer': Joint Statement," Ethics and Public Policy Center Web site (February 24, 2006), http://www.eppc.org/publications/pubID.2536/pub_detail.asp.

in the past year, as one possible method of counteracting and assuaging scientific interest in embryo-destructive research. I will not deny that we quickly saw that such a proposal might be useful to strengthen the President's pro-life strategy—and why should I deny it?[2] It is absurd, however, to suggest that this idea was developed *solely* to provide "political cover" for a President who, in any case, is no longer running for office.

But if we grant for the sake of argument that the ANT-OAR proposal contributed to shoring up the administration's pro-life strategy, could Byrnes really have a problem with this?

Most disappointing, however, is that Byrnes asserts as fact what is entirely an open question. Writes Byrnes:

> The only difference between ANT-OAR and using stem cells from IVF embryos is that the decision not to allow the embryo to develop further is made *in advance* in the case of ANT-OAR.

But clearly this begs the question. Byrnes assumes as fact that ANT-OAR, if done with human cells, would *necessarily* produce a human *embryo*, an embryonic human organism. Byrnes simply asserts without evidence that ANT-OAR would create "genetically engineered human embryos (albeit defective ones) for medical purposes."

No scientist has yet attempted ANT-OAR on even the lowliest laboratory mouse—it is, as Byrnes himself affirms, a "completely speculative procedure." But in that case, how can he purport to know with certainty what the outcome would be if done with human cells? Attempts at over-expression of Nanog prior to nuclear transfer might, indeed render an intact embryo, or they might render a highly defective embryo that limps along through a few cell divisions before expiring—*or* they might render something that we can clearly and consistently identify as something other than an embryo. Laboratory trials on ANT-OAR using animal cells will bring us a lot closer to an answer.

Byrnes says that he, and others, "entertain serious doubts that ANT-OAR could ever work scientifically," meaning he doubts the procedure could ever yield scientifically useful pluripotent stem cells. It is interesting, however, that to support his doubts he footnotes two critiques of Dr. Hurlbut's original ANT proposal, which called for a knock-down of the *Cdx2* gene. Byrnes rightly notes that ANT-OAR is a very closely related variation of this experiment. So it is rather surprising that Byrnes fails to note the study by Rudolf Jaenisch that was published in the journal *Nature* in January 2006,[3] which gave proof of principle that Hurlbut's originally proposed ANT experiment actually works, that *Cdx2* inactivation in mice can result in scientifically useful pluripotent cells. It is still a toss up whether ANT-OAR will likewise produce pluripotent cells, but the Jaenisch experiment, along with other recent research, would appear to bode well for ANT-OAR.

Byrnes does cite an article by Davor Solter that raises questions about the Jaenisch study—including the question whether it will reliably avoid producing an embryo if attempted in humans. But even Solter admits that "there is no reason why this technique should not work in humans."[4] The point of Solter's op-ed piece is not to raise doubts about the scientific feasibility of ANT-type approaches to obtaining pluripotent cells, but rather to criticize Jaenisch for "manipulating science for the sake of politics."[5] I find it frankly disturbing that Byrnes also cites a critique by Douglas Melton, a Harvard researcher who consistently dismisses the ben-

[2] Joan Frawley Desmond has explored the political utility of ANT-OAR for the Bush administration's pro-life agenda, in "Anti-Science: Pro-life Dream Team Confronts Embryonic Stem- Cell Juggernaut," *Crisis* (January 2006), http://www.crisismagazine.com/january2006/desmond.htm.

[3] A. Meissner and R. Jaenisch, "Generation of Nuclear Transfer-Derived Pluripotent ES Cells from Cloned *Cdx2*-Deficient Blastocysts," *Nature* 439.7073 (January 12, 2006): 212–215.

[4] D. Solter, "Politically Correct Human Embryonic Stem Cells?" *New England Journal of Medicine* 353.22 (December 1, 2005): 2323.

[5] Ibid.

efits of adult stem cell research and who is now aggressively pursuing human cloning at his Harvard laboratory.

I will conclude my response with the following reaffirmation of our continued support for ANT-OAR as formulated at a recent gathering of a number of the signers of the original proposal:

> In light of recent research further delineating the very early processes that control the transition from totipotency to pluripotency during mammalian embryonic development,[6] we are in agreement that immediate, constructive, and ethically acceptable research (using animal models) can be pursued that will significantly clarify the prospects of obtaining cells with properties equivalent to those of human pluripotent stem cells. This research will be within the parameters already outlined in earlier proposals for ANT/OAR research, specifically focusing on the strong determination of the pluripotent state for a nuclear-transfer derived cell by means of transcription factor regulation/overexpression, including the possibility that functional deletion of developmental genes like *Cdx2* in the somatic nucleus may be able to assist in modifying regulatory loops for these factors. By limiting and carefully constraining the reprogramming power of the oocyte through these approaches, such that a totipotent cell is precluded as a reprogramming outcome, it may be possible to directly derive a cell that is the functional equivalent of a pluripotent stem cell. Considering the scientific, medical, political, and social benefits to be gained by this research, we recommend that it be supported and pursued by all those desirous of the advances of human embryonic stem cell research without the creation or destruction of human embryos.[7]

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[6] See, for example, K. Deb et al., "*Cdx2* Gene Expression and Trophectoderm Lineage Specification in Mouse Embryos," *Science* 311.5763 (February 17, 2006): 992–996; H. Niwa et al., "Interaction between Oct3/4 and Cdx2 Determines Trophectoderm Differentiation," *Cell* 123.5 (December 2, 2005): 917–929.

[7] Addendum of April 27, 2006, to "A Joint Statement on Oocyte Assisted Reprogramming" (June 30, 2005), Westchester Institute for Ethics and the Human Person, http://www.westchesterinstitute.net/articulos/articulo.phtml?se=38&ca=22&te=12&id=35.