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by

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This past summer, President George W. Bush vetoed his first Congressional bill, the Embryonic Stem Cell Enhancement Act (H.R. 810) sponsored by Representatives Diana DeGette (D-Colorado) and Michael Castle (R-Delaware). The bill was one part of a three-part package of stem cell-related bills that was passed by the U. S. Senate and voted on by the U.S. House of Representatives; the other two bills were the Fetus Farming Prohibition Act sponsored by Senator Sam Brownback (R-Kansas) and a bill promoting alternative, presumably ethically-acceptable methods of deriving pluripotent stem cells. The centerpiece of this last bill, which was sponsored by Senators Rick Santorum and Arlen Specter (both R-Pennsylvania) and strongly backed by President Bush but which ultimately was not passed by the House of Representatives, was a controversial experimental proposal known as "altered nuclear transfer-oocyte assisted reprogramming," or ANT-OAR. This essay aims to tell the story of the ANT-OAR proposal, from its conception by Professor William Hurlbut of the President's Council on Bioethics to its adoption and promotion by a group of conservative, mostly Catholic philosophers, theologians and scientists – to its eventual demise in Congress. It also will give some reflections on how ANT-OAR promotes a genetically deterministic view of the human organism and can lead down a slippery slope into a future in which human cloning and human genetic engineering are more acceptable. For these reasons, it will be argued, ANT-OAR should be opposed by all who are against human genetic modification regardless of their political orientation.

Conception and Early Development of ANT

To understand ANT-OAR, one must first understand its parent, altered nuclear transfer, or ANT. The idea to use human "partial developmental trajectories" for medical therapy, which is what ANT proposes to do, is the brainchild of William Hurlbut, a member of the President's Council on Bioethics and a Consulting Professor at Stanford University. One of the first occasions on which the concept of ANT was discussed publicly was the July 24-25, 2003, meeting of the council.[1] In a fascinating dialogue with Professor Rudolph Jaenisch of M.I.T. and others, Hurlbut first deftly dispensed with Jaenisch's rival proposal that a human "clonote" – a cloned human individual – is not a true representative of the species and therefore can ethically be used to derive stem cells. Then, addressing the council, Hurlbut established his pro-life credentials, and masterfully introduced his own, not-so-different proposal – ANT – for deriving stem cells. Hurlbut proposed to use genetic engineering and somatic cell nuclear transfer (cloning) to create an embryo-like entity that was designed *from the beginning* to self-destruct after the blastocyst stage. Thus, ANT replaced regular cloning, which would produce, according to Jaenish's argument, an embryo that is only *statistically* likely to be highly defective and therefore not a true member of the species; ANT would *guarantee* that the embryonic entity would be defective. Such a guarantee was necessary because Dolly, who clearly was a sheep, was proof that regular cloning could, at least in some cases, produce a true member of the species.

Formally unveiled by Hurlbut at the December 3, 2004, meeting of the President's council,[2] ANT differs from regular cloning in that it involves the pre-transfer genetic alteration of the somatic cell nucleus that is to be transferred. Using what is known as RNA interference technology, the idea is to knock down the gene for a factor essential for development beyond a certain stage. Hurlbut chose the developmentally important transcription factor Cdx2 as the target for knockdown since Cdx2 is known to be essential for formation of the embryo's trophectoderm,[3] which eventually becomes the placenta, and without which an embryo cannot implant. More specifically, ANT involves introduction of a transgene that encodes an agent (a short RNA molecule) that targets and destroys the Cdx2 RNA transcript. In this manner, Cdx2 is effectively eliminated from the embryo. The absence of Cdx2 eventually leads to the embryo's demise, but this does not happen until just after the blastocyst stage when the inner cell mass containing the sought-after stem cells forms. Until the blastocyst stage, the embryo develops essentially normally. After extraction of the stem cells from the inner cell mass, the transgene that was introduced earlier can be excised, restoring the normal genotype; this eliminates any unintended side effects in the stem cells due to an absence of Cdx2. The

cells then can be grown in culture, and coaxed to differentiate into various tissue types for use in medical research or therapies.

Hurlbut knew that, in order for ANT to be acceptable to conservative religious leaders and politicians – which would be essential for broad societal acceptance – it would be necessary to have a convincing argument that the ANT-derived entity was *not* a human embryo. To make this argument attractive to classically-trained moral theologians and philosophers, Hurlbut needed a way to connect the defective embryo to a concept they understood. That connection was provided by *teleology*, the Aristotelian idea that a developing organism is intrinsically oriented toward attaining the adult form. Thus, by this reasoning, a human embryo has moral status because it has the potential to develop into an adult. Conversely – and this is key – an entity that does *not* have the potential to develop further along its trajectory, i.e. one that can go through only a *partial trajectory*, would not be human. Thus, Hurlbut argued that the ANT-derived entity, like a teratoma (an aberrant product of the fertilization process) for example, would have "no inherent principle of unity, no coherent drive in the direction of the mature human form, and no claim on the moral status due to a developing human life."[4] Like a teratoma, then, the ANT-derived entity would not be an embryo. In other words, because of a fatal genetic flaw, albeit one that would not be felt until later in the embryo's development, the ANT entity would not really be an embryo.

There were a number of early supporters of the original ANT proposal. One was Archbishop William Levada of San Francisco, who recently was appointed by Pope Benedict XVI to head the Vatican's Confraternity for the Doctrine of the Faith. In 2004, Levada wrote a letter to President Bush expressing his support for ANT.[5] Other supporters were Princeton University professor Robert George, a member of the President's Council with Hurlbut; biologist and Dominican priest Nicanor Austriaco of Providence College; Eric Cohen of the Ethics and Public Policy Center; Rev. Thomas Berg, LLC, Executive Director of the Weschester Institute for Ethics and the Human Person; and E. Christian Brugger of the Institute for Psychological Studies in Arlington, Virginia.

Despite this initial strong support, a number of philosophers and theologians had almost immediate misgivings about ANT. Among these were David Schindler, Academic Dean of the John Paul II Institute for Studies on Marriage and Family at Catholic University and U.S. editor of the international Catholic journal *Communio*; and *Communio* Associate Editor Adrian Walker. An intense theological and philosophical debate on the morality of ANT ensued in the pages of *Communio* and the *National Catholic Bioethics Quarterly*, a journal published by the National Catholic Bioethics Center in Philadelphia. While the details of this debate are beyond the scope of this essay, much of it was concerned with whether or

not a mechanistic-reductionistic description is sufficient to define the embryo, and the correct meaning of the Aristotelian-Thomistic axiom *agere sequitur esse,* "acting follows being," which both sides accepted as true, Walker, in particular, argued that ANT was "cloning with a twist," that it was simply the cloning of a severely disabled embryo. Much of this debate can be found on the *Communio* website[6] and in the Spring and Summer 2005 issues of the *National Catholic Bioethics Quarterly*. In addition to these philosophical attacks on the morality of ANT, the scientific feasibility and ethical tractability of the proposal suffered a number of criticisms from scientists, including Douglas Melton, George Daley and Charles Jennings of Harvard University, and Davor Solter of the Max-Planck Institute of Immunobiology in Frieberg.[7]

Developmental Changes Lead to ANT-OAR

The original ANT proposal has weathered the scientific criticisms, mainly because of an elegant set of experiments performed by Jaenisch and Alexander Meissner, also of M.I.T., which showed that ANT can work, at least in mice.[8] Nevertheless, even after extensive debate, the problems with ANT as a morally-acceptable means of deriving stem cells for therapy proved intractable for some. In an attempt to resolve the impasse that had arisen over the ethical acceptability of ANT, a conference was convened in Washington, D.C., in April 2005.[9] A number of Catholic and other Christian scientists, moral theologians and ethicists were present. After some deliberation, a document endorsing a new procedure, called "altered nuclear transfer-oocyte assisted reprogramming" or ANT-OAR, was formally adopted and signed by thirty-five persons in attendance. The thirty-five who signed this Joint Statement[10] included members of the Christian Pro-Life elite, as well as a number of scientists, including Austriaco, Marcus Grompe of the Oregon Stem Cell Center, Kevin FitzGerald of Georgetown University, and Maureen Condic of the University of Utah.

The essential difference between ANT-OAR and the original ANT proposal is that ANT-OAR aims to eliminate the "time gap" inherent in ANT, the time interval between the original nuclear transfer event and the point in the blastocyst stage at which the absence of Cdx2 (for example) becomes manifest, causing the embryo to lose its structural integrity. During this interval, the embryo would, for all intents and purposes, be normal. The Joint Statement proposed closing the time gap by introducing *ab initio* a "pluripotency factor" (the transcription factor Nanog was suggested) that would work together with the oocyte's cytoplasm to reprogram the somatic nucleus to be that of a pluripotent stem cell – hence the name "oocyte-assisted-reprogramming." In this manner, the totipotent

one-celled embryonic stage would be bypassed altogether. The newly-cloned entity would, from the moment of transfer, exist in a pluripotent state.

Despite these efforts at resolving the impasse, Schindler and Walker, now joined by Jose Granados of the John Paul Institute and others, were not satisfied that the ethical issues were resolved.[11] They argued that even if the time gap were collapsed to zero, the ontological status of the embryo would not change. Furthermore, the time gap was not in fact zero because some time was needed for the reprogramming process to occur. Of course, all of this assumed that ANT-OAR could even work from a scientific perspective, a doubtful proposition since, although Nanog is known to *maintain* pluripotency in stem cells,[12] there is no evidence that it could single-handedly *establish* it in the different cellular context of a newly-cloned embryo. Recently, it has become evident that a combination of factors may be needed for true reprogramming of a differentiated adult cell to the pluripotent state.[13] Finally, the prospect of reprogramming an adult cell directly by exposing it to a cocktail of factors in this manner essentially negates the need for ANT-OAR, whose goal is to generate the very same type of stem cell. Thus, if reprogramming can work – and there is mounting evidence that it can – then ANT-OAR is entirely unnecessary. The rationale for having ANT-OAR disappears.

Premature Death?

From its very inception, ANT (and ANT-OAR) was designed, in part, to achieve a political objective. Opinion polls had shown that most Americans supported using leftover embryos from IVF clinics to obtain embryonic stem cells for medical research. Increasingly, President Bush and other Republican politicians who opposed such research were under attack by scientists and citizens' groups for standing in the way of urgently-needed medical therapies. Thus, they needed a way to show that they were not antiscience or antimedicine. ANT-OAR provided a perfect solution to this problem; by supporting it, these politicians could demonstrate that they were both pro-life *and* pro-science. Indeed, both Representative Roscoe Barlett's (R-Maryland) bill H.R. 3144 and the companion senate bill S. 1557 were known as the "Respect for Life Pluripotent Stem Cell Act of 2005."[14] There is evidence that the Bush administration was kept informed about developments in the ANT-OAR debate from the beginning. ANT-OAR proponents readily admit to this political motivation; they see no reason why any possible means should not be employed in trying to advance the agenda of the Bush administration, which they see as pro-life.[15]

This past summer, as the U. S. Congress voted on the companion bills S. 1557 and H.R. 3144, all of the hopes of the ANT-OAR "Pro-Life Dream Team"[16] would either come to fruition by these bills' passage, or

would be dashed by their failure. The team's hope was that the president would veto H.R. 810 (which would allow surplus IVF embryos to be used to obtain stem cells) and sign H.R. 3144, which mandated the N.I.H. to fund methods for deriving stem cell lines "without destroying human embryos." At first, it appeared that things were going to work out as hoped. The senate passed its versions of both H.R. 810 and H.R. 3144, as well as Brownback's anti-fetal farming bill; the three bills were part of an agreed-upon package that would be passed *in toto* or not at all.[17] But in the House everything fell apart. H.R. 810 was passed but, surprisingly, H.R. 3144 fell short of the two-thirds majority vote needed for passage under the suspended House rules that were in effect.[18]

In the end, only two bills arrived on Bush's desk, the anti-fetal farming bill, which he signed, and H.R. 810, which he vetoed. Although he had hoped to counterbalance his veto of embryonic stem cell research with the signing of H.R. 3144, this was not to be the case. His hopes of being seen as pro-science as well as pro-life were not fulfilled. Bush expressed his disappointment in comments at the East Room veto-signing ceremony, and also praised the failed alternative bill, which he said would have "authorized additional federal funding for promising new research that could produce cells with the abilities of embryonic cells, but without the destruction of human embryos."[19] In an attempt to salvage what he could, he asked the Health and Human Services and the N.I.H. to "aid the search for stem cell techniques that advance promising medical science in an ethical and morally responsible way." Thus, in the end, the legislation authorizing ANT-OAR was not signed into law. Like the embryo it had sought to create, the ANT-OAR proposal apparently was only a "partial trajectory," having met its premature death in the halls of Congress.[20]

Looking Back

In reflecting on the ANT-OAR story, a question arises. Why would religious and political leaders whose stated goal was to protect human life support a proposal to genetically engineer and clone human embryos? The reasons are probably various, but at least two come to mind. First, in their zeal to promote the conservative political agenda, they might have failed to see that acceptance of ANT-OAR could lead down a slippery slope to a Brave New World in which human cloning and human genetic engineering are commonplace. Indeed, once human cloning technology is perfected through ANT-OAR, what would stop its application to embryos that are to be transferred to a mother's womb for gestation and birth? In other words, once the technology for human cloning is developed through ANT-OAR, it is a very short step to reproductive cloning. And, while ANT-OAR proponents might protest that ANT-OAR is not cloning, the truth or

falsehood of their argument is, in a certain sense, irrelevant because *cloning technology* will be used in ANT-OAR. The somatic cell nuclear transfer technology to be used for ANT-OAR and the technology that would be used for reproductive technology are *one and the same*.[21] Moreover, although one could argue that society could simply pass a law banning the transfer of cloned embryos to the womb, we all know that the current socio-economic and legal situation is really not this simple. In our pluralistic and free-market-driven society in which some parents will want to enhance the genetic makeup of their children, the very availability of human genetic engineering and cloning predictably will lead to the implementation of these technologies in the fertility clinic. One has to ask, then: Why were the ANT-OAR proponents so blind to these future possibilities? Could it be that their political ambitions clouded their vision?

Second, at least some proponents of ANT-OAR may have embraced Hurlbut's (and others') philosophical view that the embryo, and indeed every organism, is defined by its genetic makeup. For, if a human embryo is denied membership in the species *Homo sapiens* because it has an engineered genetic defect, then this means that we all are defined by our genetic composition. This statement is an articulation of a belief in genetic determinism, which says that our identity is determined by our genes. Of course, although common, the belief in genetic determinism has been and still is a salient force in the eugenic practices of the past and those of the present. While a deterministic view is patently false from a biological perspective – indeed, systems biology is revealing that organisms are holistic systems that cannot be defined as the sum of their parts[22] – the falsehood of this view has not stopped it from permeating society. Nevertheless, it is disturbing to hear genetic determinism being espoused by religious leaders, who should be aware of the social dangers associated with it.

Conclusion

It is imperative that all persons who are opposed to human genetic modification and human cloning – whether Christian or not, liberal or conservative, in favor of embryonic stem research or opposed to it – join together in defeating ANT-OAR and any future proposals that promote human cloning. Moreover, opposition is essential whether proposals of this sort originate from the political right or the political left.[23] For, all such proposals that sanction human cloning, including ANT-OAR, will pave that way into a future in which the commodification of human life for medical ends is socially acceptable. Who among us would want this to happen?

References

1. See the transcript of the 24-25 July 2003 meeting of the President's Council on Bioethics, session 3. Available at:
http://bioethicsprint.bioethics.gov/transcripts/july03/session3.html
Last accessed 9-17-06.

2. William Hurlbut, President's Council on Bioethics, "Session 6: Seeking Morally Unproblematic Sources of Human Stem Cells," transcript, December 3, 2004. Available at: http://www.bioethics.gov/transcripts/dec04/session6.html Last accessed 9-17-06.

3. K. Chawengsaksophak, W. de Graaff, J. Rossant, J. Deschamps, and F. Beck, "Cdx2 is Essential for Axial Elongation in Mouse Development," *Proceedings of the National Academy of Sciences USA* 101 (18 May 2004): 7641-7645.

4. Hurlbut, President's Council, session 6 transcript, December 3, 2004.

5. Mentioned in Jocelyn Dong, "The Line Between Faith and Science: Stanford Professor Hopes to Further Stem Cell Research Without Destroying Human Embryos," The *Palo Alto Weekly - online edition* (26 October 2005). Available at:
http://www.paloaltoonline.com/weekly morgue/2005/2005_10_26.stemcell26.shtml
Last accessed 9-17-06.

6. Available at: http://www.communio-icr.com/ant.html Last accessed 9-17-06.

7. See D.A. Melton, G.Q. Daley, and C. G. Jennings, "Altered Nuclear Transfer – A Flawed Proposal," *New England Journal of Medicine* 351 (30 December 2004): 2791-2792; and D. Solter, "Politically Correct Human Embryonic Stem Cells?" *New England Journal of Medicine* 353 (1 December 2005): 2321-2323.

8. A. Meissner, and R. Jaenisch, "Generation of Nuclear Transfer-Derived Pluripotent ES Cells From Cloned Cdx2-Deficient Blastocysts," *Nature* 439: 212-221.

9. For a description of this conference, see E. Christian Brugger, "Ethical Commitment Stimulates Scientific Insight," *National Catholic Bioethics Quarterly* 5.3 (Autumn 2005): 445-446.

10. See "Production of Pluripotent Stem Cells by Oocyte-Assisted Reprogramming: Joint Statement with Signatories," *National Catholic Bioethics Quarterly* 5.3 (Autumn 2005): 579-583. Also available online at the Ethics and Public Policy website at:
http://www.eppc.org/publications/pubID.2374/pub_detail.asp
Last accessed 9-17-06.

11. Articles in the continuing debate can be read at the *Communio* website at http://www.communio-icr/ant.htm See also the Autumn and Winter 2005 and the

Summer 2006 issues of the *National Catholic Bioethics Quarterly*, and the article Byrnes, W. M. and J. Granados, "ANT-OAR Fails on all Counts: Method of Harvesting Stem Cells Riddled with Scientific and Ethical Flaws," *Science and Theology News* (June 2006): 23-25.

12. I. Chambers, D. Colby, M. Robertson, J. Nichols, S. Lee, S. Tweedie, and A. Smith, "Functional Expression Cloning of Nanog, a Pluripotency Sustaining Factor in Embryonic Stem Cells," *Cell* 113 (30 May 2003) 643-655; and K. Mitsui, Y. Toluzawa, H. Itoh, K. Segawa, M. Murakami, K. Takahashi, M. Maruyama, M. Maeda and S. Yamanaka, "The Homeoprotein Nanog is Required for Maintenance of Pluripotency in Mouse Epiblast and ES Cells," *Cell* 113 (30 May 2003): 631-642.

13. K. Takahashi and S. Yamanaka, "Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors," *Cell* 126 (25 August 2006): 1-14.

14. The texts of these bills can be found online at:
http://www.govtrack.us/congress/billtext.xpd?bill=h109-3144
http://www/govtrack.us/congress/billtext.xpd?bill=s109-1557
Last accessed 9-17-06.

15. See Fr. Thomas Berg's reply to W. Malcolm Byrnes, "Inconsistencies on the Pro-ANT-OAR Position," *National Catholic Bioethics Quarterly* 6.2 (Summer 2006): 201-205.

16 This name was given by Joan Frawley Desmond in her article "Pro-Life Dream Team Confronts Embryonic Stem-Cell Juggernaut," *Crisis Magazine* (January 2006): 25-31. Available at
http://www.crisismagazine.com/january2006/desmond.htm

17. Rick Weiss, "Senate to Consider Stem Cell Proposals," *The Washington Post* (30 June 2006): A5.

18. See Robert Novak, "Stem Cells: No One-Two Punch," The *Washington Post* (24 July 2006): A19. Novak describes the high drama that unfolded as the "Republican high command" in the House struggled to pass H.R. 3144. He also gives the names of specific Republican congressmen who "defected," voting against the bill.

19. Whitehouse Press Release on July 19, 2006, "President Discusses Stem Cell Research Policy." Available online at:
http://www.whitehouse.gov/news/releases/2006/07 20060719-3.html.
Last accessed 7-21-06.

20. Or has it? ANT was moved forward in large part by the sheer strength of the personality of William Hurlbut. There is evidence that Hurlbut has no intention of being deterred by the recent defeat of ANT-OAR in Congress. Indeed, he apparently

envisions an expanded role for developmental biology in medicine in the future, a role that will increasingly make use of human "partial developmental trajectories." See W.B. Hurlbut, "Framing the Future: Embryonic Stem Cells, Ethics and the Emerging Era of Developmental Biology," *Pediatric Research* 59: 4R-12R.

21. Some of the ANT-OAR supporters were highly critical of human cloning researcher Woo Suk Hwang of South Korea. However, it is deeply inconsistent to condemn cloning technology on one hand, and promote it – via ANT-OAR, which uses cloning – on the other. See: T. Berg, "Cloning, After Hwang." The *National Catholic Register* (24 February 2006). Available at http://www.ncregister.com/aticulo2.php?artkod=MTc4

22. Stuart Newman, "The Fall and Rise of Systems Biology: Recovering from a Half-Century Gene Binge:' *Genewatch* 16 July-August 2003): 8-12.

23. An example of a similar proposal originating from the political left is the ballot initiative (Amendment 2) that, unfortunately, was passed by the citizens of Missouri in the recent mid-term elections held on November 7, 2006. The amendment proposes to *ban* human cloning, but what it actually does is to *promote* human cloning, making the cloning of a human embryo to obtain stem cells a constitutional right in Missouri. How can the amendment actually legalize cloning when it claims to ban it? By defining cloning in such a way that using somatic cell nuclear transfer (SCNT) to create a human embryo without "implanting" it is not cloning. Specifically, according to the amendment, to "'clone or attempt to clone a human being' means to implant in a uterus or attempt to implant in a uterus anything other than the product of fertilization of an egg of a human female by a sperm of a human male for the purpose of initiating a pregnancy that could result in the creation of a human fetus, or the birth of a human being." [See http://www.sos.mo.gov/elections/2006petitions/ppStemCell.asp. Last accessed 11-08-06.] As an open letter signed by more than two dozen scientists, ethicists, physicians and law experts (including this author) points out [See the Do No Harmwebsite at http://www.stemcellresearch.org/press/2006-11-01_MO.htm Last accessed 11-08-06], this definition of human cloning is not the commonly accepted one, nor the one given by the President's Council on Bioethics in their authoritative report on the subject [*Human Cloning and Human Dignity*, Leon R. Kass, ed. (New York: Public Affairs, 2002)]. On the contrary, it is one that misleads and deceives. It serves to trick Missouri voters into thinking that they are voting against human cloning when, in fact, they are voting *for* it. How is this proposal similar to ANT-OAR? Both present definitions of human cloning that deny the reality of what is actually being done – creating a cloned *human* embryo (a defective one, to be sure, in the case of ANT-OAR). In the case of the Missouri amendment, the assumption of its supporters is "if it *does not* implant, it is not human." In the case of ANT-OAR supporters, the assumption is "if it *cannot* implant due to an inherent defect, it is not human." Thus, the two proposals are similar in many ways.