“One Small Island of Unity in a Sea of Controversy”

Altered Nuclear Transfer and the moral boundaries of humanity.

Q&A by Kathryn Jean Lopez

William B. Hurlbut, M.D., is a physician and consulting professor in the program in human biology at Stanford University. He's best known as a proponent of "Altered Nuclear Transfer," which, as Ramesh Ponnuru explained here would create "biological entities that have some of the properties of embryos, but are not living organisms."

Research in *Nature* magazine earlier this fall highlighted "Altered Nuclear Transfer" possibilities as an alternative to embryonic-stem-cell research, plagued as the latter is in ethical problems.

National Review Online editor Kathryn Lopez recently discussed ANT with Dr. Hurlbut. Here's what he said.

NATIONAL REVIEW ONLINE: What is so significant about the "Altered Nuclear Transfer" announcement in *Nature* earlier this fall? It seemed hot-but-confusing news for a few days there.

DR. WILLIAM B. HURLBUT:

Although this study was done on mice, it raises the realistic prospect of a positive resolution of our nation's impasse over human-embryonic-stem-cell research.

NRO: In layman's terms, what is ANT and why is it potentially so promising?

DR. HURLBUT: Altered Nuclear Transfer seeks a morally acceptable means of producing pluripotent stem cells (the functional equivalent of embryonic stem cells) without the creation and destruction of human embryos. ANT would provide a technological way to answer the current ethical and legislative impasse over federal funding of new human-embryonic-stem-cell lines. By current practice, new lines are derived from the disaggregation of embryos "left over" from in-vitro fertilization clinics (IVF) or directly created by cloning (SCNT). Federal law specifically prohibits funding of any practice that endangers or destroys a human embryo.

ANT would employ the basic technology of nuclear transfer (SCNT), but with an alteration such that no embryo is created, yet pluripotent stem cells are produced.

In standard nuclear transfer (popularly known as "therapeutic cloning") the nucleus of an adult cell is placed into an egg cell that has had its nucleus removed. The egg, which now carries a full set of DNA from an adult, is electrically stimulated and starts to divide like a naturally fertilized egg from which an embryo develops. This is how Dolly the sheep was produced.

ANT uses the technology of nuclear transfer, but with a preemptive alteration that assures that no embryo is created. The adult-cell nucleus is first altered before it is transferred into the egg. The alteration causes the adult-cell DNA to function in such a way that no embryo is generated, but pluripotent stem cells are produced.

An embryo is "totipotent," capable of forming an organism, but embryonic stem cells are "pluripotent," capable of forming all the cell types of the body but not in the organized and coordinated pattern of a living being. ANT would directly create cells that are pluripotent but not totipotent.

There is a natural precedent for such a project. An ovarian tumor (called a "teratoma") appears to produce embryonic stem cells as well as later stage cells and body tissues. But the tumor is a disorganized growth, like a bag of jumbled puzzle parts, and lacks the character of an organism. Neither medical science nor the major religious traditions have ever considered these growths to be "moral beings" worthy of protection, yet they produce embryonic stem cells.

ANT is a broad concept with a range of specific approaches. The study by Rudolf Jaenisch involved the silencing of a gene crucial for early organization. Although the popular press portrayed the alteration as preventing the formation of the placenta, the failure of formation is at a far more fundamental level. The silenced gene, known by the name "Cdx2," is essential for the first cell differentiation and without it no basic body axes or body plan are ever established. It is reasonable to consider this alteration not

a "deficiency" in an existing being, but an "insufficiency" that precludes the coherent organization that is the very defining character of an embryo.

There are other genes or combinations of genes that might also be used in ANT. One recent proposal, called ANT-OAR (oocyte-assisted reprogramming), would involve fast-forwarding gene-expression patterns directly to those that characterize embryonic stem cells. By "jump-starting" gene expression, one goes directly to a differentiated cell state and bypasses entirely the earlier developmental stages. This idea, put forward by Markus Grompe, director of the stem-cell program at Oregon Health Sciences, is the subject of current scientific research.

NRO: Let's say the science of it works. Isn't ANT a little too confusing — Is it or isn't it an embryo? — to ever make an impact on public policy?

DR. HURLBUT: I don't think ANT is, in its basic concept, too difficult for the average person to understand. Most of us live in a world of technological marvels that we barely understand; as long as the fundamental moral principles are clear, I think there will be a wide acceptance of a solution that allows positive progress in biomedical science.

The controversy over embryonic stem cells is a complicated matter with passionate feelings on both sides. To some extent there is a broader battle going on between conflicting world views. Yet, **clearly, both sides in this difficult debate are defending important human goods. And both of these goods, opening avenues of advance in biomedical science and preserving the fundamental moral principles on which our society is based, are important to all of us. I believe that with constructive conversation and creative use of our emerging powers over developmental biology, we can meet the concerns of both sides — a true win-win solution**. Several proposals have been put forward to solve this impasse, but only ANT and direct reprogramming of adult cells seem

capable of meeting the moral concerns while providing ES cell lines with a full range of genetic types including "customized" cell lines from specific patients for study of disease and maybe one day personalized therapy.

Some say that adult cells such as those obtained from bone marrow or umbilical-cord blood can do many of the same things as embryonic stem cells. This may be true, and we should vigorously investigate the powers of these cells. But, to date, these claims have not been established, so this is an open matter. Others maintain that embryonic stem cells are too difficult to control and will never meet all the promises that have been made to argue that it is justifiable to destroy human embryos to advance medical cures. This too may be true, but if there were no moral objections we would definitely want to study these interesting cells.

It is important to recognize that neither adult stem cells, nor the direct reprogramming of adult cells back to a pluripotent state would allow us to do the same studies that we will want to do with embryonic stem cells. To see why this is true we need to get some perspective on where we are in the saga of our advancing science. We have sequenced the human genome and are beginning to study the proteins that are coded by the genes. From here on out our science will be about developmental biology, how the proteins and other cell components assemble into living beings.

If we are to study human embryology, we will need new tools that allow us to investigate every stage of development, but without the creation and destruction of human embryos. Projects such as ANT will allow us to do this by creating partial and incomplete subsystems of organic growth that do not have the full integrated development that characterizes a living organism. This will be a difficult transition in our social consciousness since we have a natural inclination to associate the dynamics of organic change with the moral meaning of living beings. But tumors, such as teratomas, also undergo a kind of development.

In the previous century we came to recognize that neither cells such as blood, nor tissues such as skin, nor whole organs such as hearts are the locus of human moral meaning. Likewise, in this age of developmental biology, we will come to recognize that the laboratory creation of partial trajectories of organic growth are not a violation of the moral concerns our fundamental principles are seeking to protect.

NRO: How enthused are moral thinkers you talk to about ANT?

DR. HURLBUT: There is wide openness to this project among leading moral philosophers and religious authorities. When I first began to formulate this proposal, I talked with many scholars and scientists to make sure the ideas were sound. A little more than a year ago I met with Archbishop Levada, who was at that time chairman of the United States Conference of Catholic Bishop's Committee on Doctrine (he has subsequently been appointed Prefect of the Sacred Congregation for the Doctrine of the Faith [former home to Cardinal Ratzinger, now Pope Benedict]. He was very encouraging and after we met wrote a letter to President Bush in support of further exploration of these ideas.

I think everyone involved recognizes that the ANT proposal raises unfamiliar and difficult issues, and there is need for a broad and thoughtful dialogue before proceeding to human studies. Some have expressed concerns about one or another specific approach to ANT, but for the most part, I think these have come from an inadequate understanding of the science.

It is important to keep in mind that ANT is a broad concept with many possible specific approaches. Last April we held a conference where we gathered leading scholars and scientists to discuss these ideas. It was from that dialogue that ANT-OAR emerged. This led to the release of a document signed by 35 leading scientists, moral philosophers, and religious authorities in support of this version of Altered Nuclear Transfer. I am confident that

with a constructive dialogue and creative use of our advancing technology we can find an approach that gains consensus support.

NRO: Is it only pro-life type scientists who are pursuing ANT?

DR. HURLBUT: No, there is interest in ANT by scientists with a range of views including some who do not have moral concerns about the instrumental use of human embryos in the first 14 days. These scientists recognize both the pragmatic prospects of the ANT project in opening new lines of ES cells for federal funding, and also acknowledge the importance of a positive pluralism that sustains social consensus for public support of research in the biomedical sciences.

Some scientists have tried to denigrate the feasibility of the ANT project and others have labeled it a "distraction." There seems to be a narrow agenda behind such pronouncements, not an open disposition to truly seek a solution that takes seriously the concerns of all of our fellow citizens. Depending on how the questions are framed, somewhere between 60-80 percent of people in the United States are against the intentional creation and destruction of human embryos. This is the position of, for example, Senate Majority Leader William Frist. A purely political victory by either side will leave our country bitterly divided. I believe that a positive solution such as ANT would open a better future for biomedical science.

NRO: You've spent a good deal of energy talking to politicians about these issues. Do you have any real hope cloning — including so-called therapeutic cloning — will be banned in the U.S.?

DR. HURLBUT: At this point, it is unclear which way things will go in the long term, but it seems obvious there will be no new ES-cell lines available for federal funding within the next three years. **My goal in putting forward ANT is to seek a positive resolution of one aspect of our nation's impasse; to establish one small island of unity in a sea of controversy. With such a solution to our immediate practical problem, we might be in a better position to carefully work out a broader frame for the future of biomedical science.**

Our current argument over ES-cell research is just the first symbolic battle as we enter the era of research in developmental biology. We need to address the fundamental moral concerns that this science poses or there will be an endless series of conflicts that will either stall science or infringe on basic principles of human dignity. Chimeras, parthenogenesis, reaggregation of differentiated cells into organ systems (including brain tissues) — these all require that we define with clarity and precision the moral boundaries of humanity. I think the future holds very positive prospects if we now consider these matters within a respectful dialogue that honors the insights of all of our fellow citizens.

NRO: Why is it that news like ANT and other alternatives to embryonic-stem-cell research don't get more coverage — both media and financial?

DR. HURLBUT: Well, several factors go into this. For one thing, promises play better than prudence and moral principles — -we like to hear what we want to hear.

Also, there is an established bias in some reporting — -though I have to say that I have encountered some very honorable journalists. I see the bias though because I take the time to explain the scientific basis for the ANT project and then it is directly mischaracterized or misrepresented.

For example, some insist on calling the product of ANT a "disabled embryo," even in their headlines. That mischaracterizes the intention of the

project as well as the opinion of many scientists and moral philosophers that no embryo is created. Even if one wants to argue that this issue has not been fully resolved, it is not right to preempt the dialogue by giving a label to what is produced before the matter is even discussed.

My sense is that some see the ANT proposal and other "alternative sources" (as well as progress with adult stem cells) as a danger to their specific agendas on these matters, and that doesn't lead to very good reporting. Beyond that, I think we need to acknowledge the scientific difficulty of this subject. Even many well-educated people are confused about embryonic-stem-cell research, and this is exacerbated by the intentional obfuscation and changing terminology that has characterized this debate.

NRO: What would you like every American to know about ANT?

DR. HURLBUT: Altered Nuclear Transfer is a hopeful proposal that can honor the positive goods being defended by both sides of this difficult debate. Such a solution would be in keeping with the American spirit and a triumph for our nation as a whole.

NRO: How significant is the resignation of South Korean cloner Hwang Woo-suk?

DR. HURLBUT: I think this situation is very significant, with far-reaching implications for both embryonic-stem-cell research and efforts to establish international standards for research ethics.

I talked with Dr. Hwang when he was here at Stanford last June. I found him straightforward and congenial, with a certain warmth and humility in his personal manner. I am saddened by the revelations that have come forth in the past few weeks.

In his formal presentation at Stanford, Dr. Hwang stated, "I would like to express my deep heartfelt thanks and gratitude to all our voluntary oocyte donors." Now he has acknowledged using eggs from two graduate students working in his lab and from at least 20 women paid for "donating" their eggs — -and he has admitted lying about these matters. The medical procedure

used to obtain eggs, known as super-ovulation, is invasive and painful and can cause serious side effects and, in rare cases, even death. When lab subordinates and "payment for product" are involved, words such as "volunteer" and "donor" would seem to lose their normal meaning.

The significance of this situation reaches beyond the immediate events. A spokesman for the South Korean health ministry has said, "the donations were made according to values consistent with Eastern culture and shouldn't be looked at from the standpoint of Western culture." Indeed, *Nature* magazine reports that Hwang's colleague, Roh Moo-hyun explains that one of the graduate students "felt obliged to donate after making mistakes early in the experiment that wasted eggs and set the team back by months. "I think it's a beautiful story," Roh told *Nature*.

But from his side, Dr. Hwang has said plainly that he is deeply ashamed of his actions. This admission, and the fact that he felt it was necessary to lie about these matters in the first place, suggests that more than cultural differences were operating here. Hwang has admitted that the importance of the scientific goals and a sense of ambition blinded him to the ethical concerns. Transparency and truth are at the heart of both ethics and science, and must transcend any personal pride or supposed difference in cultural perspective. The very idea of cooperative international collaboration depends on this.

We are at the early edge of a revolution in our understanding and control of basic biology. The significance of this revolution and its practical implications are matters, not of national interest or commercial competition, but of the most fundamental human concern. As an editorial in the *JoogAng Daily* rightly pointed out, the values and principles governing this research must be something other than the "economic value worth ten times or more than that generated by semiconductors."

Considerations of national competition are often expressed by our own scientists and journalists. They argue that if South Korea and other countries are forging forward with embryo-destructive research, we must overcome the political impasse that prevents federal funding for exploration of this new realm of science.

The ethical objections that are at the heart of this impasse are often dismissed as the private beliefs of America's "scientifically ignorant"

religious Right. Word has it that Dr. Hwang is holed-up in a temple outside of Seoul. Will he too now be accused of mixing science and religion?

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