Essays

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Why Human "Altered Nuclear Transfer" Is Unethical

A Holistic Systems View

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A remarkable event occurred at the December 3, 2004, meeting of the U. S. President's Council on Bioethics. Council member William Hurlbut, a physician and Consulting Professor in the Program in Human Biology at Stanford University, formally unveiled a proposal that he claimed would solve the ethical problems surrounding the extraction of stem cells from human embryos.[1] The proposal would involve the creation of genetically defective embryos that "never rise to the level of integrated organismal existence essential to be designated human life with potential,"[2] and therefore could be used as morally acceptable sources of stem cells for research and therapy. Only a few of the council members (Paul McHugh, Gilbert Meilaender and, to some extent, Michael Gazzaniga) expressed concern about Hurlbut's proposal, and Leon Kass, council chairman, endorsed the proposal "at

The views expressed in this essay are solely the author's. They do not necessarily reflect the views of Howard University.

[1]Note that Dr. Hurlbut actually put forth this proposal (without indicating a specific gene to knock out) for the first time in 2002. (See William Hurlbut, "Statement of Dr. Hurlbut," in *Human Cloning and Human Dignity: An Ethical Inquiry* [Washington, DC: The President's Council on Bioethics, 2002], 267–276; http://bioethicsprint.bioethics.gov/reports/cloningreport/appendix.html#hurlbut.)

[2]William Hurlbut, President's Council on Bioethics, "Session 6: Seeking Morally Unproblematic Sources of Human Stem Cells," transcript, December 3, 2004, http://www.bioethics.gov/transcripts/dec04/session6.html.

least in principle" and entertained the idea that it might be "a morally fruitful possibility for the nation."[3]

Notwithstanding the overall upbeat mood of the President's Council on December 3, the aim of this essay is to show that Hurlbut's proposal does not solve the ethical problems associated with human embryonic stem cell research. Two major reasons will be presented. First, the proposal, which involves modification of a somatic cell nucleus, suffers from an ethical problem that is common to all types of human genetic engineering: since the procedure is not foolproof, there will be failures. In the case of the procedure Hurlbut proposes, some normal (albeit cloned) embryos will be produced. Second, as Richard Doerflinger of the U. S. Conference of Catholic Bishops hinted in his comments at the end of the meeting, the embryo engineered in the manner described is, at least in the early stages of its development, fully human despite its genetic defect. This essay also will show that a reasonable person might mistakenly view the proposal as legitimate if he or she makes the error of conflating genetic determinism with Aristotelian teleology. Finally, it will argue that ethical clarity can be achieved by seeing the embryo as a holistic entity possessing emergent properties that cannot simply be spelled out by genes.

Two Major Flaws

In describing his proposal, Hurlbut explained that the embryonic entity created would lack "the essential elements for embryological development but [contain] a partial developmental potential capable of generating embryonic stem cells."[4] The idea would be to delete from a somatic cell a gene essential for development beyond a certain stage. The altered nucleus of the somatic cell then would be transferred into an enucleated egg using "altered nuclear transfer," or ANT, which uses the techniques of somatic cell nuclear transfer (SCNT, or cloning).[5] The modified single-celled embryo created by ANT would be allowed to undergo cleavage and differentiation to the blastocyst stage. Embryonic stem cells from the inner cell mass of the blastocyst then could be extracted, corrected for the genetic defect, and stimulated in culture to grow and differentiate into various tissue types. Such cells potentially could be used for therapies or research. Hurlbut gave *cdx2* as an example of a developmental gene that could be deleted, and then later reinstalled.[6] *Cdx2* is ex-

[3]Leon Kass, "Session 6" transcript.

[4]Hurlbut, "Session 6" transcript.

[5]The only difference between ANT and ordinary SCNT (cloning) is that, for ANT, the somatic cell is altered by some sort of genetic engineering (RNA interference was mentioned; gene knock-out is also a possibility) prior to being transferred into the enucleated egg. For ordinary SCNT, the somatic cell nucleus is not altered—unless one considers the alteration that occurs when the nucleus is partially "reprogrammed" epigenetically by the egg cell into which it is transferred. Thus, it seems that ANT could fall under the category of "human genetic engineering," which involves a cloning step.

[6]Hurlbut has stressed that *cdx2* is only an example, and that other genes or sets of genes may prove to be more appropriate for knock-out or knock-down to achieve the desired result—an entity that self-destructs after forming the all-important inner cell mass along with its trophectoderm. Nevertheless, the critical characteristic of the gene that is deleted is that

pressed at the 16- to 32-cell stage in mice, and is important for integrating pathways involved in axis elongation and anterior-posterior patterning in the developing mouse (and human) embryo.[7] The absence of *cdx2* results in a "visibly abnormal blastocyst" that has a poorly defined trophectoderm, or outer layer, but the stem cells in the inner cell mass are presumably unaffected.[8]

Embryos engineered in this way would "fail to establish even the most basic features of human organismal infrastructure."[9] Such entities 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*."[10] According to Hurlbut, they would be similar to naturally occurring entities such as ovarian teratomas and hydatidiform moles, both of which develop in a disorganized manner due to chromosomal abnormalities and defects in genomic imprinting.[11] The reason-

its deletion must not impair the formation of healthy, pluripotential stem cells in the inner cell mass. Thus, any embryo that is useful as a source of stem cells would seem to have to go through a normal developmental trajectory at least to the stage at which the inner cell mass is formed. Any embryo that is defective from the beginning (*ab initio*) will be scientifically and medically useless.

[7]Kallayanee Chawengsaksophak et al., "*Cdx2* Is Essential for Axial Elongation in Mouse Development," *Proceedings of the National Academy of Sciences USA* 101.20 (May 18, 2004): 7641–7645.

[8]Hurlbut, "Session 6" transcript.

[9]Ibid.

[10]Ibid. (emphasis added).

[11]Both ovarian teratomas and hydatidiform moles are aberrant products of mis-fertilization. Ovarian teratomas (also called ovarian dermoid cysts) are maternal in origin; they arise from the spontaneous (parthenogenic) activation of an egg—without a sperm. Mature ovarian teratomas can contain various body parts (hair, teeth, limbs) embedded in a disorganized mass of tissue. Hydatidiform moles are either complete or partial. Complete moles form when a single sperm fertilizes a nucleus-free egg (followed by duplication of the paternal genome). Partial moles occur when two sperm jointly fertilize an egg. Both complete and partial moles involve aberrant growth of the trophoblast (trophectoderm). Some partial moles contain a malformed fetus, but complete moles never do. (For more information, see P. Vassilakos, "Pathology of Molar Pregnancy," http://www.gfmer.ch/Books/Reproductive_health/Mole.html.) In both teratomas and moles (and also in clones), there are errors in genomic imprinting, i.e., the patterns of epigenetic markings from the father and mother that affect gene expression during development. This is because maternal or paternal chromosomes are either absent or underrepresented. In a normal embryo that has genetic contributions from both father and mother, imprinting is normal: some paternal genes are turned off and some maternal genes are turned on (or vice-versa) at a particular time and place. There is carefully coordinated regulation of gene expression during development that depends, in part, on imprinting patterns. However, in teratomas, paternal imprinting is absent; in moles, maternal imprinting is reduced or absent.

A detailed discussion of the similarities and differences between teratomas or moles and ANT-derived embryos is beyond the scope of this essay. Nevertheless, there is one obvious difference between them: how they arise. Whereas the former are "accidents of nature," the latter are *intentionally created*. Leon Kass has written about how a principle of

ing might go like this: since no one would consider an ovarian teratoma or a hydatidiform mole a human being, neither should the ANT-derived embryo be considered human.

The first flaw in Hurlbut's proposal stems from the fact that it involves a human genetic engineering procedure. The proposal calls for the knock-out (or knock-down using RNA interference technology) of an essential developmental gene, for example *cdx2*, from the somatic cell that is to be inserted into an enucleated egg. After the embryo develops, forming a blastocyst that is abnormal in its outer layer but normal in its inner cell mass, stem cells can be isolated and the missing gene later "reinstalled." One question that arises is: how will one know if the gene of interest (say, *cdx2*) has truly been deleted, and is absent in the developing embryo? How will one know if the procedure has worked? The answer is that the cloned embryos will have to be tested. What, then, if the genetic tests reveal that the procedure has failed? What if the gene has not been successfully deleted in one or more of the embryos? Will not these embryos be considered fully human with full moral status in Hurlbut's view?[12] Even if the developmental gene selected for deletion is clearly functionally conserved among mammals (thus showing that it should work the same way in both humans and mice), and even if the procedure is perfected in animal models before it is used in humans, there still is the possibility that the procedure will not work perfectly every time. Such failures are part of the very fabric of science; they are part of the reason why human genetic engineering in general is inherently unethical.[13] The "altered nuclear transfer" procedure that is at the core of Hurlbut's

"repugnance" can guide our moral response to human cloning (Leon Kass, "Why We Should Ban Cloning Now: Preventing a Brave New World," *The New Republic Online* [May 17, 2001], http://www.tnr.com/052101/kass052101.html). One can ask: Is not the idea of creating an intentionally defective human entity for the sole purpose of harvesting stem cells repugnant? Indeed, this response seems so obvious that even some proponents of embryonic stem cell research find Hurlbut's proposal distasteful. An example is found in an essay by William Saletan ("Monster Farming: The Creepy Solution to the Stem-Cell Debate," *Slate* [December 5, 2004], http://slate.msn.com/id/2110670/). It would be tragic if, out of zeal to circumvent the ethical problems associated with obtaining stem cells from human embryos, one resorted to doing something that was equally unethical.

[12]Hurlbut's view of the moral status of the human embryo is revealed in the following statement he made at the December 3 council meeting: "I, as everybody in the council knows, have stood very strongly for the principle that human life is present from conception. When I looked at the scientific facts … I looked as plainly as I could and I simply could not think—could not agree that the early embryo was, as some scientists are saying, an inchoate clump of cells. It's a living whole human being." (transcript)

[13]"Human genetic engineering" is defined here as the artificial modification of the genetic makeup of a human individual through the production of a genetically modified human embryo. ANT is a type of human genetic engineering procedure. All genetic engineering procedures, including ANT, involve the testing and screening of the embryos that are produced in order to see if they have the desired genetic alteration. Presumably, embryos that do not have the desired alteration—and there will be some—will be discarded. For this reason, all human genetic engineering procedures are unethical. Please note that the author is not referring to somatic gene therapy (sometimes considered to be a type of genetic engineer-

proposal—a procedure that has a genetic engineering component—cannot escape this universal scientific rule that there will always be some experimental failures.

There is a second, even more fundamental, reason why Hurlbut's proposal is flawed, one involving the issue of gene expression. Nearly every cell in the human body has the full complement of the genes in the human genome (an exception is the erythrocyte), but not all of these genes are expressed in every tissue, or at every stage of development. During development, different genes are turned on and off at different stages, their expression rising and falling both temporally and spatially. There is a complex network of gene expression patterns, with the expression of one gene often affecting that of others. A gene may remain silent during the initial stages of embryonic development, and then be turned on at a particular time and place in the embryo. Subsequent stages of development may be highly dependent on the gene's expression. Such is the case for the important developmental gene *cdx2*, used here as an example by Hurlbut. *Cdx2* is expressed at the 16- to 32- cell stage in the trophectoderm (outer layer) but not in the inner cell mass, and *cdx2* expression is critical for the integration of downstream pathways controlling subsequent development. Before the 16- to 32- cell stage, *cdx2* is silent, not expressed. If it has been deleted, in these early stages there will be *no indication* of its absence since *its time has not yet come* to be expressed.

The question here is this: Is not the embryo prior to the stage at which *cdx2* expression is needed just like a so-called normal embryo, except for the silent "defect" lurking in its genome? And, is not this situation precisely like that of a person with a genetic predisposition for Huntington's disease who lives a symptom-free life until the age of forty? Is a person with a genetic predisposition for Alzheimer's disease an Alzheimer's patient at age twenty-five? (No.) Is a woman with the BRCA1 mutation a breast cancer patient at age fifteen? (No.) In a similar manner, one could argue that ANT-derived embryos (which are perfectly normal in every respect during the initial stages of development, except that they have genes knocked

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ing), which involves the remediation of a genetic deficiency in the somatic cells of a child or an adult. Also note that although ANT is a type of genetic engineering, it is not an example of *germline* engineering, because ANT-derived embryos never develop beyond the days-old blastocyst stage. In other words, they never develop to an embryonic stage that has differentiated germline cells (or even their precursors). Germline engineering, which is not under consideration here, is a type of genetic engineering in which an IVF-fertilized embryo is genetically altered, and then used to produce a modified embryo by nuclear transfer into an enucleated egg. The modified embryo is then allowed to develop and grow into an individual of reproductive age, so that all of the cells in his or her body, including the germline cells, contain the genetic change. This genetic change then can be passed on to future generations. (See Mario Capecchi, "Human Germline Gene Therapy: How and Why," in *Engineering the Human Germline: An Exploration of the Science and Ethics of Altering the Genes We Pass Onto Our Children*, eds. Gregory Stock and John Campbell [New York: Oxford University Press, 2000], 35.) Germline engineering has its own set of ethical problems. (Please see W. Malcolm Byrnes, "The Ecological Imperative and Its Application to Ethical Issues in Human Genetic Technology," *Ethics in Science and Environmental Politics* [2003]: 63-69, available at http://www.int-res.com/articles/esep/2003/E36.pdf).

out of their genomes) are indeed human embryos. Just as a fifteen-year-old girl who has a genetic predisposition for breast cancer does not have breast cancer at age fifteen, an ANT-derived embryo is not abnormal in its early stages of development.

From these arguments, one can see that Hurlbut's proposal is deeply flawed. The truth is that there is no easy way around the ethical problems that are associated with embryonic stem cell research and human cloning. Unfortunately, a scientific or technological "trick" cannot provide us with a solution.

Genetic Determinism

One might ask: why did the council by and large accept Hurlbut's proposal? More to the point, why did a council that previously had supported a moratorium on human cloning execute an apparent about-face and support a proposal to clone genetically engineered human embryos? There are a number of possible reasons. First, the members surely could see the scientific and medical promise of embryonic stem cells; if Hurlbut's proposal could offer an acceptable way around the ethical problems associated with obtaining them, it was worth trying. Also, they likely wanted to give their colleague a fair chance; they wanted to be receptive. Finally, the council had been under intense pressure from the scientific community, having been accused fairly recently of being biased against science.[14] They may have wanted to extend an olive branch to scientists.

Yet, there could be another, more underlying reason why the proposal was accepted: there is a strong tendency in our society to accept the tenets of *genetic determinism*, which holds that living things are defined by their genes. The council members are no less influenced by this prevailing scientific view than the rest of us. Along with this, there might have been a temptation for some members to combine genetic determinism with Aristotelian teleology.

To see the hand of genetic determinism at work in Hurlbut's proposal, one need only reflect on the argument that was made. The argument was that if the embryo has a fatal genetic flaw, it is not human. Indeed, it never was human, even in the early stages of development before the flaw revealed itself. Rather, such an embryo is a "biological entity that … from its very beginning lacks the attributes and

[14]In March 2004, the Union of Concerned Scientists (UCS) leveled the charge that the Bush administration had dismissed two members, replacing them with more conservative ones, in order to stack the council in favor of administration policies. This charge was part of a larger UCS report, signed by over five thousand scientists (including this author), that presented evidence that Bush administration policies ignore scientific findings in a broad range of areas, including global warming and the environment (Union of Concerned Scientists, *Scientific Integrity in Policymaking: An Investigation into the Bush Administration's Misuse of Science* [March 2004], http://www.ucsusa.org/documents/RSI_final_fullreport.pdf; an excerpt from the July 2004 update to the report pertaining to the President's Council on Bioethics is available at http://www.ucsusa.org/global_environment/rsi/page.cfm?pageID=1446). Leon Kass denied the charge that the council is biased in an op-ed piece (Leon Kass, "We Don't Play Politics with Science," *Washington Post* [March 3, 2004]: A27). Indeed, there is no direct evidence that it is.

capacities of a human embryo."[15] The key phrase here is *from the very beginning*. Since the embryo *from the very beginning* has a defect lodged in its genome that will later render it unable to develop further, it cannot be human. Never mind that the defect has not yet been expressed. All that matters is that it is in the genome. Thus, genetic makeup is the defining principle of biological identity. This is a clear case of someone believing that genes determine who or what one is; it is a clear application of a belief in genetic determinism.

Aristotle[16] believed that living organisms, including humans, strive to fulfill their innate potential as they grow and develop. This striving has a teleological orientation. By this thinking, human embryos should be respected because they possess the potential to become fully formed adults; this potential is inherent in their very being. Conversely, it would seem to follow that if an ostensibly human embryo does not have the *potential* to develop into an adult, it is not human and does not have moral status. In the case of Hurlbut's proposal, properly designed embryos such as those lacking *cdx2* almost without a doubt could not progress beyond the blastocyst stage. They could not progress very far at all through the developmental process, let alone hope to become adults. How could they be called human, then? Clearly, this is the question with which the council members were grappling.

This combination of a belief in genetic determinism with a belief in Aristotelian teleology was particularly evident at the December 3 meeting in the statement by member Robert George. Lending his support to Hurlbut, George said:

> Now, when I ask myself why are we so sure that a teratoma is not a whole living member of the species *Homo sapiens*, why are we so sure we can distinguish the teratoma from the embryo, my conclusion is that the teratoma, unlike the embryo, lacks … from the start and always, the active disposition for self-organization and self-directed development in the direction of human maturity.[17]

We see here the view that genetic makeup confers potential, that a set of genes confer "the active disposition for self-organization and self-directed development in the direction of human maturity." But, this view, common though it might be in our society, is incorrect.

Biological science today tells us that genes alone are not the central controllers of biological form and function.[18] Rather, what are important in this regard are

[15]William Hurlbut, "Session 6" transcript.

[16]Aristotle is best known for his philosophy. Yet, he was also a path-breaking embryologist. He wrote a comprehensive five-volume compendium of embryology, *On the Generation of Animals*, the first ever written, according to Needham (Joseph Needham, *A History of Embryology* [New York: Abelard-Schuman, 1959]: 39). He dissected the embryos of many different animals, and grappled with the issues of epigenesis and preformationism, issues that would come to dominate embryology in subsequent centuries. Of Aristotle, Needham wrote: "The depth of Aristotle's insight into the generation of animals has not been surpassed by any subsequent embryologist, and, considering the width of his interests, cannot have been equaled." (Ibid., 42)

[17]Robert George, "Session 6" transcript.

[18]See W. Malcolm Byrnes, "Epigenetics, Evolution, and Us" (*The National Catholic Bioethics Quarterly* 3.3 [Autumn 2003]: 489–500), which presents some of the scientific evi-

genes acting in the cellular, organismal, and environmental *context*. Genes, or any other parts for that matter, do not confer biological identity; rather, identity is conferred by the whole. The truth is that living systems are *holistic*;[19] they have properties that are emergent, that are dependent on the integrated whole. Thus, living systems cannot be adequately described in terms of parts and interactions among parts. This is true at each level of organization within an organism: at the cellular, tissue, and whole organismal levels. For this reason, systems biology,[20] even though it justifiably will become an important tool for drug development and drug screening, for example, will never be able to completely describe a living system—neither an embryo, nor a tissue, nor even a bacterial cell. Living systems are nonlinear and exceedingly complex, and the levels of complexity render inadequate even the most sophisticated DNA or protein microarray platforms and computer software programs. What all of this means is that one cannot conclude that an ANT-derived embryo is not human based on the presence or absence of a genetic characteristic. It is human by virtue of the fact that, at least in the first few days of its existence—until the absence of *cdx2* is felt—it moves through a normal *human* developmental trajectory; it is highly complex and has emergent properties.[21]

Guidance from Nature

If genetic determinism and reductionistic systems biology cause us to go down the wrong path, tricking us into thinking that a technology such as human "altered

dence that it is not genes *per se*, but rather the genome in context, that is important in biological development and in evolution.

[19]Some biologists prefer to use the term "organic" rather than holistic because holism is sometimes taken to include vitalism, which has a nonmaterial basis. Organicism is essentially materialistic holism. Gilbert and Sarkar describe organicism in this way: With organicism, "complex wholes are inherently greater than the sum of their parts in the sense that the properties of each part within the whole are dependent upon the context of the part within the whole in which they operate." (Scott F. Gilbert and Sahotra Sarkar, "Embracing Complexity: Organicism for the 21st Century," *Developmental Dynamics* 219.1 [July 25, 2000]: 1–9).

[20]It should be pointed out that the term "systems biology" can be used in reference to two very different kinds of scientific investigation. The first is what can be termed *reductionistic* systems biology; it is the kind that most people, including William Hurlbut, Dominican priest Nicanor Austriaco ("On Static Eggs and Dynamic Embryos: A Systems Perspective," *The National Catholic Bioethics Quarterly* 2.4 [Winter 2002]: 659–683) and Leroy Hood, director of the Institute for Systems Biology, mean when they use the term systems biology. In this case, there is the belief that if one can describe in sufficient detail all of the parts of a living system and how they interact, one can completely describe the system. The other kind can be termed *holistic* systems biology; it is the kind that people such as biologist Stuart Newman (Stuart A. Newman, "The Fall and Rise of Systems Biology," *GeneWatch* 16.4 [July–August 2003]: 8–12) mean when they use the term systems biology. In this second case, there is a focus on the whole system *as opposed to* its parts, and the whole system has properties that are emergent. The two terms mean very different things. Because most people do not distinguish between them, there is often confusion about what actually is being communicated.

[21]The reader might object at this point and say: "Wait a minute: Is not the integrity of the whole compromised in an ANT-derived embryo? If a part (an essential gene, say) is miss-

nuclear transfer" is ethical, where can we find genuine guidance? What can help direct us to do what is ethical? One answer is: *the natural world itself*.

Although our modern technology may lead us to think otherwise, we humans do live within a global natural ecosystem. We have evolved in intimate contact with other life forms on earth (and with the abiotic environment) in the ever-changing web of life. Our genome, which is a record of our species' evolutionary story, reveals our relatedness to earth's other life forms, each of which has its own distinct but related story. The developmental trajectories of the embryos of various species of animals, including our own, share amazing similarities—and fascinating differences. The embryos of all species, though different, are propelled forward through unique and complex developmental processes with a certain momentum because they have the emergent property called *life*. Genes play critical roles in these processes, as do nongenetic (*epi*genetic) factors. Physical forces also are important as cells differentiate and aggregate into tissues.[22] The complexity of these developmental processes is so great that, despite advances in systems biology, we cannot really grasp what life is; we cannot adequately capture living systems or define them.

We are deeply connected with all living creatures and, indeed, with the whole natural world. Because of this, nature can give us general guidance regarding what is ethically right in terms of how we should treat our fellow human beings. What, then, can nature tell us about Hurlbut's proposal? It tells us that an ANT-derived embryo, just like any other living creature, has an inherent "will" to live. It has an intact developmental trajectory in its first few days of life. Although burdened with a genetic time bomb that eventually will destroy its ability to develop further, it will strive to continue on in existence, to grow and develop. The spark of life, which was present from the beginning of its clonal existence, still is present. Life, the emergent property, is there. It is a living, *human* embryo. To create such an entity, knowing full well that it will self-destruct later, would be unethical.

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ing, how can the embryo function as a whole? Does not an acknowledgment of the importance of complexity *support*, not refute, Hurlbut's argument?" The answer to this last question indeed would be "yes" if the effect of the missing part (e.g., the *cdx2* gene) was manifest from the very beginning. The answer is "no," however, because we know that *cdx2* expression is silent until the 16- to 32-cell stage. In terms of the functioning of the whole, then, the situation is just as if the part (*cdx2*) were present. The problem for Hurlbut is this: An embryo that is not able to proceed along a normal trajectory for at least an early period of development—for example up to the blastocyst stage—is worthless to science and medicine. An "embryo" that is so grossly defective that it cannot even begin its development would have an extremely fleeting existence; it could be said to hardly exist at all. There appears to be no way around this paradox.

[22]For a discussion of this fascinating topic, see the book *Origination of Organismal Form: Beyond the Gene in Developmental and Evolutionary Biology*, edited by Gerd B. Muller and Stuart A. Newman (Cambridge, MA: MIT Press, 2003). See also the recent scientific article "Surface Mechanics Mediate Pattern Formation in the Developing Retina," by Takashi Hayashi and Richard W. Carthew (*Nature* 431.7009 [October 7, 2004]: 647–652).