ANT-OAR: A Morally Acceptable Means for Deriving Pluripotent Stem Cells. A Reply to Criticisms

• **E. Christian Brugger** •

"If the cell's behavior is not
commensurate with that of an embryo,
the cell is not an embryo."

In December 2004, Dr. William Hurlbut, physician and professor at Stanford University and a member of the President's Council on Bioethics, presented a proposal to the Council entitled "Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells."[1] Hurlbut's premise stated that, using modern cloning technology, it may be scientifically

[1]Hurlbut published an expanded version of the essay with the same title in *Perspectives in Biology and Medicine* 48, no. 2 (Spring 2005): 211–228; for a synopsis of the idea, see Hurlbut's interview with Jennifer Lahl, National Director of the Center for Bioethics and Culture Network, entitled "Altered Nuclear Transfer: Is it the Answer for the Embryonic Stem Cell Research Debate?" available at www.cbc-network.org.

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possible to produce embryonic-like (i.e., pluripotent[2]) stem cells *without ever creating and destroying human embryos*. Cloning is accomplished by using somatic cell nuclear transfer (SCNT), in which the nucleus of a somatic (adult body) cell is removed and transferred into an enucleated oocyte (i.e., an egg cell with its nucleus removed). The crucial difference between SCNT for purposes of human cloning and SCNT as proposed by Hurlbut is that in the latter procedure, the genetic material in the somatic cell nucleus is preemptively altered *before* nuclear transfer in such a way as to create biological conditions incompatible with the coming into existence of embryonic human life, but compatible with the development of pluripotent stem cells. He called his broad conceptual proposal Altered Nuclear Transfer (ANT).

In June 2005, a group of thirty-five scholars (including ethicists, moral theologians, physicians, and scientists), including Dr. Hurlbut, published a joint statement proposing a specific type of ANT called Oocyte Assisted Reprogramming (ANT-OAR).[3] ANT-

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[2]"Pluripotency" is the capacity of a cell to develop into all the various tissue types of the human body. It is important to note that presently *no useful embryonic stem cell-based therapies exist*. Nonetheless, many scientists believe that embryonic stem cells, because of their pluripotency, promise to provide important tools for the study of disease, and possibly to provide cells and tissues for groundbreaking medical therapies.

[3]The joint statement was published as: "Production of Pluripotent Stem Cells by Oocyte-Assisted Reprogramming: Joint Statement with Signatories," *National Catholic Bioethics Quarterly* 5, no. 3 (Autumn 2005): 579–583. It should be emphasized that the proposal called for initial research using only nonhuman animal cells. Only in the case that such research established beyond a reasonable doubt that ANT-OAR could reliably be used to create pluripotent stem cells *without creating embryos* would its signatories support research using human cells. Signatories include: Hadley Arkes, Ph.D., Amherst College; Rev. Nicanor Pier Giorgio Austriaco, O.P., Ph.D., Providence College; Rev. Thomas Berg, L.C., Ph.D., The Westchester Institute for Ethics and the Human Person; E. Christian Brugger, D. Phil., Institute for Psychological Sciences; Nigel M. de S. Cameron, Ph.D., Institute on Biotechnology and the Human Future and Chicago-Kent College of Law, Illinois Institute of Technology; Joseph Capizzi, Ph.D., Catholic University of America; Maureen L. Condic, Ph.D., University of Utah, School of Medicine; Samuel B. Condic, M.A., University of Houston; Rev. Kevin T. FitzGerald, S.J., Ph.D., Georgetown University Medical Center; Rev. Kevin Flannery, S.J., D.Phil., Pontifical Gregorian University; Edward J. Furton, Ph.D., The National Catholic Bioethics Center; Robert P. George, J.D., D.Phil., Princeton University; Timothy George, Th.D., Samford University; Alfonso Gómez-Lobo, Dr. phil., Georgetown University; Germain Grisez, Ph.D., Mount Saint Mary's University; Markus

OAR begins from the assumption that the identity and function of each cell in the human body depends on the precise interrelation, communication, and on-off pre-programming of the approximately thirty thousand genes in the cell's genome. This condition of cell interaction and expression is called the cell's "epigenetic state" (or "genetic imprinting"). The epigenetic state of the single-celled human embryo (or zygote) is totipotent, that is, it has the developmental capacity to differentiate in an orderly and coordinated way into all the tissue types necessary for full organismal development, including into the placenta, umbilical cord, and other extra-embryonic tissues. From the perspective of epigenetics, we might say that totipotency defines a human zygote. It follows that it is reasonable to conclude that where there is a totipotent human cell, there is a human zygote.

Cloning technology, drawing on this reasoning, has developed a way to "reprogram" the epigenetic state of a cell. Using SCNT, scientists have observed that the cytoplasm of an enucleated oocyte has a remarkable capacity to transform the epigenetic state of a transferred diploid nucleus from its original state to a state of totipotency. The nucleus at the time of transfer has the genetic imprinting of the differentiated cell type from which it was extracted (e.g., cardiac cell, liver cell, skin cell). After nuclear transfer into an enucleated oocyte, the epigenetic state is reprogrammed from its

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formerly highly specialized state back to a state of totipotency. It goes through a process of epigenetic dedifferentiation. If it reaches its terminus, the reprogrammed cell is a zygote, a one-celled embryo, with the genotype of the donor of the somatic cell. It will develop into an adult who is genetically identical to the somatic cell's donor. This is how Dolly the sheep was created.[4]

Making use of the technique of SCNT, ANT-OAR proposes to utilize the reprogramming capacity of oocyte cytoplasm. But it intends to do so without ever generating human embryos. We know something of the molecular mechanisms underlying pluripotent stem cells, including that several transcription factors are characteristic of the pluripotent state. More than characteristic, certain ones appear to be essential for establishing and maintaining the state of pluripotency.[5] One such transcription factor (and only one of a number, all of which individually or in combination, or combined with other genetic alterations, potentially would be candidates for ANT-OAR) is the homeoprotein Nanog.[6] Its expression characterizes the unique state of pluripotent cells as neither oocytes nor later differentiated cell types. Nanog is found expressed in pluripotent stem cells and not expressed in oocytes or single-celled embryos. When its expression is forced, a cell is not totipotent, but, likewise, cell differentiation is prevented. When its expression is blocked, cells rapidly begin to differentiate. The Joint Statement proposes a procedure that combines the reprogramming of the nuclear genome of a somatic cell with precise genetic alterations forcing the expression of the transcription factor Nanog (or similar factors that are required for the pluripotent state). The

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[4]It should be noted that such reprogramming is highly inefficient, with typically only 0.1-1% of all transferred nuclei producing a live birth.

[5]A transcription factor is a protein that helps regulate gene expression by binding to the gene and aiding and directing transcription of the gene's DNA into RNA. For gene expression to be complete the RNA needs to be further translated into its corresponding protein.

[6]Nanog is just one of a number of transcription factors that have been shown to be essential in maintaining the pluripotency of inner cell mass cells; for two essays on Nanog's activity, see Hatano, Shin-ya, Masako Tada, et al., "Pluripotential competence of cells associated with *Nanog* activity," *Mechanisms of Development* 122 (2005), 67–79; and Mitsui, Kaoru, Yoshimi Tokuzawa, et al., "The Homeoprotein Nanog Is Required for Maintenance of Pluripotency in Mouse Epiblast and ES Cells," *Cell* 113 (30 May 2003): 631–642.

alterations in the nuclear genome would be carried out *prior* to nuclear transfer. When the nucleus is transferred into the enucleated oocyte, we create *ab initio* a Nanog-expressing cell whose epigenetic character is that of a pluripotent stem cell and incompatible with zygotic existence. The Joint Statement recommends that ANT-OAR be explored first through experimentation utilizing nonhuman animal cells.

One critic

David L. Schindler, dean and professor of theology at the John Paul II Institute for Studies on Marriage and Family in Washington, D.C., has accused the 35 signatories of the ANT-OAR proposal of advancing a "top to bottom" mechanistic account of the origins of human life.[7] His argument goes like this: the signatories argue that the identity of any particular cell depends on its epigenetic state; if this is the case, then by altering the epigenetic state of a cell, we can alter the identity of that cell; it follows that if we make certain precise epigenetic alterations to the genome of a somatic cell nucleus before transferring it into an enucleated oocyte, the entity that we bring into existence will not be a one-celled human being (a zygote), but rather its identity will be that of the type of cell whose epigenetics we have altered it to become, i.e., a pluripotent stem cell. Schindler says this reduces the ontological reality of the entity brought into existence to its raw epigenetic map. But epigenetics, he says, does not determine the identity of a cell, it determines only a cell's observable features, i.e., its phenotype:

> Epigenetics can determine only the phenotypical manifestation of the cell whose identity is at issue, not its (ontological) identity

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[7]David L. Schindler, "A Response to the Joint Statement, 'Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming,'" *Communio: International Catholic Review* 32, no. 2 (Summer 2005): 369-380. Part II of the Spring 2005 issue of *Communio* (vol. 32, no. 1) is dedicated to Hurlbut's original ANT proposal; Schindler and Adrian J. Walker criticize Hurlbut's proposal in two essays; Nicanor Pier Giorgio Austriaco, O.P., offers a reply. Although several of the arguments and concomitant errors leveled against ANT by Schindler and Walker correspond to those formulated in Schindler's later essay, "A Response to the Joint Statement," my intention in this essay is to criticize *only* Schindler's later essay.

> as such. Thus, the mere act of modifying the epigenetic profile of the OAR product cannot be sufficient to prevent that product from being, or having been, an incipient human organism.[8]

It follows, he concludes, that ANT-OAR fails in what it sets out to produce since the proposal sets forth a procedure that "is really a means of artificially replicating conception."

There are two related errors in Schindler's reasoning. First, he argues that by asserting that the identity of a cell is determined by a cell's epigenetic state, ANT-OAR reduces ontology to epigenetics, which he calls "a classic mechanistic maneuver:"

> For what else can we call the confusion of phenotype (based on epigenetics) with substantial identity upon which the argument for OAR hinges? If, in fact, substantial identity is essentially a matter of epigenetics, then the organismic whole is no more than the sum of its parts, and the absence or presence of an organism is simply a matter of reshuffling the epigenetic pieces.[9]

Schindler here badly mischaracterizes ANT-OAR. The joint proposal does not assert, and its signatories would in fact reject, the proposition that "substantial identity is essentially a matter of epigenetics." The joint proposal states, and Schindler himself quotes it as stating, that "the nature of each cell depends on its epigenetic state." To say a cell's identity *depends* on its epigenetic state is not to say a cell's "substantial identity" is "no more than" its epigenetic state. Schindler has misinterpreted the joint proposal as putting forward epigenetic disposition as a *sufficient* condition for the actualization of embryonic life, when in fact its authors intended it only as a *necessary* condition. They do assert that the identity of a cell depends on the cell's genetic imprinting, which means that the identity of a one-celled human embryo too depends on its genetic imprinting. To deny this is to deny the biological basis for differentiation among cell types in the human body.[10] If cells are not differen-

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[8]Schindler, "A Response to the Joint Statement," 371–372.

[9]Ibid., 372.

[10]Nicanor Austriaco, O.P., writes: "if we follow Schindler's logic, any human cell—a skin cell, a liver cell, or a kidney cell—regardless of its 'phenotypical manifestation' could be ontologically equivalent to a single-cell embryo" ("Are Teratomas Embryos or Non-Embryos? A Criterion for Oocyte-Assisted Reprogramming," *The National Catholic Bioethics Quarterly* 5, no. 4 [Winter 2005]: 705f).

tiated by their respective gene expression, what biologically differentiates a skin cell from a liver cell? Not the number of chromosomes, genes, or nucleotides, nor even the DNA sequence, since in cells from the same person, these are identical. Rather, there are epigenetic conditions under which a liver cell is able to be a liver cell, and without which it *cannot* be a liver cell. Is a liver cell no more than its epigenetic state? No. But to be what it is depends necessarily (among other things) on that state. So too a zygote has precise biological conditions under which it is able to be what it is, and without which it cannot come into existence. Among other things, such conditions include an epigenetic state of totipotency. To assert this is not to assert that it is no more than its epigenetic state. Its genetic imprinting is a necessary condition, but not a sufficient condition for its identity as a human being at the zygotic phase of development.

Schindler's second and related error is philosophical. In denying that epigenetics is a necessary condition for differentiating a cell's identity, he implicitly denies that a zygote's organic bodily material is necessary for its identity as human. Why is this? Because epigenetics and organic identity are integrally connected. The epigenetic state of a cell includes the primordial preprogrammed totality of the activated, inactivated and *to be* activated and inactivated states of the genes in the cell's genome. These epigenetic primordia determine the active potentialities of that cell,[11] including in some cases the aptitude to be informed by a non-material human soul. A liver, renal, cardiac, immune, or neural cell, as well as a one-celled human embryo, is what it is, biologically speaking, not because of the presence of some given organic material per se, but precisely because of that organic material's active potentialities. If a human cell has the requisite set of active potentialities to undergo self-directed, human organismic development, then it is a one-celled embryo. To be sure, an embryo is *more* than its organic matter and epigenetic primordia; but without them, an entity is not an embryo. If a cell's active potentiality is to function like a liver cell, then it has the nature of a liver cell. And if *ab initio* it will only ever do what a liver cell does, then it was *ab initio* a liver cell. This follows from the

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[11]Austriaco discusses the concepts of active and passive potentialities in reference to ANT in "Altered Nuclear Transfer: A Critique of a Critique," *Communio: International Catholic Review* 32, no. 1 (Spring 2005): 172–176.

principle that the potentialities of a thing determine the possibilities for that thing's actuations, and hence its identity. This principle was first affirmed by Aristotle in his hylomorphic conception of the relationship between body and soul, a conception Aquinas takes up and develops.

Aristotle holds that matter and form exist together in an individuating, unified relationship. A thing's *substantial form* is what makes the thing the kind of thing it is. It is a thing's *whatness*, or essence.[12] Aristotle calls the substantial form in humans the intellectual soul. The human body gets its being as *this* kind of body—i.e., a *human* body, from the soul. Another way of saying this is, the soul is the whole body's actuality. (For the Aristotelian-Thomistic hylomorphic tradition, *form* equals actuality in a thing.) And so Aristotle writes, "the soul is an actuality of . . . a natural body having life potentially in it."[13] Saying the same thing, Aquinas writes: "the soul is the primary actuality of a physical body capable of life."[14] For the human person, this means the intellectual soul is the actuality of a material body capable of being a human body (with the presumption here that only living human bodies are, properly speaking human).[15] What does Aquinas mean when he refers to a body as

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[12]Aristotle, *Metaphysics*, bk. VII, no. 10, 1035b14, tr. W. D. Ross, in *The Complete Works of Aristotle*, ed. Jonathan Barnes, vol. 2 (Princeton, N.J.: Princeton University Press, 1984), 1635. Aquinas will also say that one sense of "form" is the "what it is" of a thing, its essence or quiddity, which would include its matter taken universally, like "flesh and bones" in the case of man. Other times, however, Aristotle and Thomas will use "substantial form" to mean only one part of a thing's essence. A natural substance is composed of both matter and form, and neither of these alone is what that substance is—a man is not just a soul. At *Metaphysics* VI, bk. 1, 1025b29–35, for example, Aristotle insists that the "what" of a natural thing must always include matter. I thank Dr. Michael Augros for pointing this out to me.

[13]Aristotle, *De Anima*, bk. II, no. 1, 412a27, tr. J. A. Smith, in *The Complete Works of Aristotle*, ed. Jonathan Barnes, vol. 1 (Princeton, N.J.: Princeton University Press, 1984), 656.

[14]Aquinas, *Commentary on Aristotle's De Anima,* bk. II, lecture IV, par. 271, tr. Kenelm Foster, O.P., and Silvester Humphries, O.P. (Notre Dame, Ind.: Dumb Ox Press, 1994), 88.

[15]Aquinas asserts that at death, when life passes from the body, a substantial change takes place; the body is no longer, properly speaking, a human body, except in an equivocal sense; the eyes and flesh of a corpse are only equivocally referred to as human eyes and human flesh since neither possesses its proper operation qua

"capable of life," and Aristotle when he says, "having life potentially in it"? Something very specific: in the case of a human being, the body must have an *active potency* to be alive in a specifically human way; the body must already *be* human in potency: "the actuality of any given thing can only be realized in what is already potentially that thing, in a matter of its own appropriate to it."[16] (*Matter* equals potentiality.) The human soul therefore is the actuality of some matter already potentially a human being. Only organic material with an active potential for humanness is informed by an intellectual soul. The constitution of the organic material is a necessary condition for human life's actualizability; and the presence of the requisite disposition is indicative of its state of being already informed by the specifically human form.[17] This means some organic material *precisely because of its active potentialities* will be incompatible with the properly human form of an intellectual soul. The organic material of a liver cell, for example, will be incompatible. Why? Not because it does not possess a diploid nucleus with a full human genome, because it does. Rather, because the epigenetic state of that genome excludes the possibility of that cell doing what humans do at that stage of existence, developing as humans develop, and hence (we conclude) excludes the possibility of being human, since, as Aquinas says, *agere sequitur esse* (action follows being). The organic constitution of a one-celled embryo, on the other hand, is by definition adequate material. Schindler's argument fails to understand that it is precisely the character of the organic material, which includes *inter alia* the material's genetic imprinting, that determines the possibilities for humanness.

Schindler might reply saying he denies nothing of what has just been said about the determining importance of the character of

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human. He says this in response to Platonic dualism, which holds that since the soul is united to the body as a driver is to a machine, the body is what it is apart from the soul; therefore at death, when the soul departs, the body remains a human body and its parts human body parts; see Aquinas, *Summa Contra Gentiles* (*SCG*), bk. II, ch. 57, no. 10, tr. James F. Anderson (South Bend, Ind.: University of Notre Dame Press, 1975), 171.

[16]Aristotle, *De Anima*, bk. II, 414a25.

[17]The idea of *materia apta* is not that we have, in one instance, the proper organic matter, and *then* the soul that comes to inform it, but rather, evidence of a characteristically organismal disposition of the matter bespeaks the presence of the in-forming substantial human form.

the material. If we grant him this, it becomes clear that his account of what constitutes *materia apta* for the actualization of humanness is badly flawed. He writes:

> OAR presupposes an actual fusion of an oocyte and a somatic cell nucleus, and thus mimics conception. This is true even if the genesis of the new entity and its pluripotent stem-cell-like manifestation occur simultaneously, or with no apparent time interval at all. What OAR proponents call the "epigenetic reprogramming" of the somatic cell nucleus by the oocyte might be more accurately called the pre-planned developmental modification of a human conceptus (brought about by artificial means).[18]

The quote illustrates that at the heart of Schindler's conception of the conditions for the coming to be of human life, is the governing erroneous assumption that the *fusion of an oocyte and a somatic cell nucleus, irrespective of the epigenetic character of the so-called "fused" entity, gives rise to a human embryo*. There are two problems with this. First, Schindler's science is flawed. It is not the "fusion" of a somatic cell nucleus and an oocyte. There is no nuclear fusion at all. The entity into which the somatic cell nucleus is transferred, because it has been enucleated, is no longer an oocyte. In fact, it is not even a cell, but rather an ooplast, a bag of cytoplasm. Transferring an altered nucleus into the ooplast does not "mimic" conception, since at conception a sperm penetrates an egg, the nuclei fuse, giving rise to a diploid zygote with a totipotent epigenetic state. Nothing like this is being proposed in ANT-OAR.

Second, if ANT-OAR produced a human embryo, then the entity created would have, or pass through, a totipotent epigenetic state. But the product of ANT-OAR *never* is totipotent nor passes through such a state. This is where Schindler's governing erroneous assumption imposes itself with particular force: "ANT-OAR . . . mimics conception . . . even if the genesis of the new entity and its pluripotent stem-cell-like manifestation occur simultaneously, or with no apparent time interval at all."[19] In other words, it does not matter if the entity created is pluripotent, it is still an embryo. This belies scientific fact. A one-celled embryo is by definition totipotent.

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[18]Schindler, "A Response to the Joint Statement," 371.

[19]Ibid.

The entity created by ANT-OAR is *ab initio* pluripotent. It therefore cannot be an embryo. But might not it pass, ever so instantaneously, through a state of totipotency during reprogramming? In principle, no. If Nanog expression (or expression of some other transcription factor, or combination of transcription factors, or combination of transcription factors and precise gene modifications, etc.) is definitional of the state of pluripotency; and forced Nanog expression (or forced expression of . . .) characterizes *ab initio* the biological "artifact"[20] that ANT-OAR brings into existence, being intentionally made to do so *before* nuclear transfer, then the entity *never* was totipotent. Further, the reprogramming to a state of pluripotency is not a process of developmental differentiation beginning with totipotency and moving to pluripotency, as with embryonic development. It is a process of *dedifferentiation* moving from the highly specified epigenetic state of the adult nuclear genome "backwards" (we might say, albeit not without some imprecision) to a state of pluripotency. It never reaches a state of totipotency, because it is intentionally prevented from doing so.[21]

Schindler may reply: your thesis may work in principle, but how can you ever verify empirically that the kind of cell ANT-OAR produces is not a human embryo? Our answer: the same way we come to know what any cell type is and is not. We perform a *material analysis*. We screen and see what genes the cell expresses. If the genes expressed are characteristic of embryo genes, then we conclude it is a zygote. If they are not, say they are identical to those expressed in liver cells, then we conclude it is not an embryo but a liver cell. We also perform a *temporal analysis*. We observe the cell's behavior over time. We see how it acts. If it acts like an embryo we

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[20]In his original proposal for ANT, Hurlbut uses the term "biological artifact" to refer to the entity created by the method, an entity, he says, "with 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" (William B. Hurlbut, "Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells," 225).

[21]Edward Furton makes this point against Schindler's argument; see Edward J. Furton, "A Defense of Oocyte-Assisted Reprogramming," *The National Catholic Bioethics Quarterly* 5, no. 3 (Autumn 2005): 467.

conclude it is an embryo.[22] If it acts like a liver cell, we conclude it is a liver cell. Schindler writes:

> Determination of the presence of life in its most subtle beginnings is precisely *not* obvious in the manner of a positivistic fact, but always involves philosophical mediation (even if only unconsciously). Apprehending life in its most subtle beginnings involves a cognitional act that is not only empirical but also (at least implicitly) metaphysical in nature, an act which, rightly exercised, recognizes the mystery characteristic of the organism in its very givenness. . . . God gives the organism to itself and so creates an originality that by definition we *cannot* know or control exhaustively, an originality that we therefore should not attempt or claim to know or control exhaustively.[23]

I see no problem affirming—if I understand Schindler—that we cannot "exhaustively" know and control the "originality" of life, if by originality he means having its unique, irrepeatable origin ultimately in God. And certainly we should not attempt to "exhaustively" control human life's origin. But according to Schindler's logic, we can *never* know through empirical observation—which I take him to mean by the term "positivistic fact"—that a human cell is or is not a human embryo. This is absurd. We can know the difference between a one-celled embryo and a liver cell because the cells express different genes and act differently: *agere sequitur esse*. If we transplant a liver cell into a female uterus, it does not do what a human embryo does when transplanted in a female uterus. If the cell's behavior is not commensurate with that of an embryo, the cell is not an embryo. To deny that science is able to apprehend such fundamental biochemical and behavioral cell distinctions, and to apprehend them with certitude, is to operate from a doubt that can only be termed irrational. Schindler has severed the link between what something is and our ability to know what it is. This implies an erroneous epistemology, one which denies that human intelligence, even weakened by sin, can attain to a

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[22]The idea that we know what a thing is by observing how it behaves is more fully developed in Maureen L. Condic and Samuel B. Condic, "Defining Organisms by Organization," *The National Catholic Bioethics Quarterly* 5, no. 2 (Summer 2005): 331–353, esp. 339–340.

[23]Schindler, "A Response to the Joint Statement," 375.

certain knowledge of reality.[24] Further, if the embryo cannot manifest itself bodily in any observable way, then this implies the embryo is something other than its body, i.e., that a human being can be present without bodily manifestation. This is dualism and is inconsistent with sound reasoning and Catholic moral teaching: "it [dualism] contradicts the *Church's teachings on the unity of the human person,* whose rational soul is *per se et essentialiter* the form of his body."[25] John Paul II affirms that the "spiritual and immortal soul is the principle of unity of the human being, whereby it exists as a whole—*corpore et anima unus*—as a person."[26] If the human person subsists in a body-soul unity, then human activity, including zygotic activity, will always also be bodily activity. As bodily activity it will be observable and knowable. By what criteria does Schindler assess the ontological identity of an entity of human origin? What tells him the ontological identity if not the physical characteristics?

SCNT: ANT-OAR is different

Schindler is worried because the technique used in ANT-OAR (namely, SCNT) is the same technique that is used in human cloning. And in human cloning a one-celled embryo is created. But why do we, or Schindler, or anyone know that using SCNT for purposes of cloning human embryos does or can create a human embryo? Because when it is done, we sometimes get an entity that behaves like an embryo. We know the entity from what it does, and we draw our conclusions accordingly. We will know ANT-OAR *does not* create an embryo and therefore does not "mimic conception," because we do not get an entity that expresses itself and acts like an embryo. Scientists did not conclude *a priori* that SCNT

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[24]John Paul II rejects this view in his 1998 encyclical *Fides et ratio;* there he strongly affirms "the human capacity to *know the truth*, to come to a knowledge which can reach objective truth by means of that *adaequatio rei et intellectus* to which the Scholastic Doctors referred" (82, Vatican translation). Vatican II also teaches: "intelligence is not confined to observable data alone, but can with genuine certitude attain to reality itself as knowable, though in consequence of sin that certitude is partly obscured and weakened" (*Gaudium et spes*, 15, Vatican translation).

[25]John Paul II, *Veritatis splendor* (1993), 48, Vatican translation. Emphasis original.

[26]Ibid.

creates embryos; they concluded that it creates embryos because when it was carried out with that intention, it sometimes worked. If it did not work, nuclear transfer for purpose of creating pluripotent stem cells would be, I presume, non-controversial. It seems that Schindler has stigmatized all forms of nuclear transfer with a sort of mysterious embryo-creating power simply because SCNT for purposes of cloning human embryos sometimes works. The fact that in ANT-OAR a diploid nucleus is transferred into an enucleated oocyte is not sufficient ground for concluding the entity that arises possesses the active potentiality to undergo organized, self-directed development in a way characteristic of a human being. Parthenotes, teratomas,[27] and certain kinds of hydatidiform moles[28] begin as oocytes with diploid nuclei. We can even make a hydatidiform mole: enucleate an oocyte and transfer into it the nuclei of two sperm cells. We get an oocyte with a diploid nucleus. Have we made a zygote? Nor can Schindler fall back on the ambiguous term "fusing of oocyte and somatic cell nucleus." We can "fuse" an enucleated oocyte and a somatic cell nucleus in a high speed blender. Do we get an embryo? The constituents after all are very much "fused." We can "fuse" sperm and eggs in a blender. Have we mimicked conception? No. How do we know? Because we do not get an entity that expresses itself in any recognizable way like an embryo. But if the "fusion" of sperm and egg in a blender resulted in entities that behaved like human embryos, if they went on to divide, differentiate, express the biochemical patterns of human embryos, *then we would conclude that such a procedure gives rise to human embryos*. It is absurd to claim that an entity is a human organism when it expresses itself neither materially nor temporally in ways characteristic of human organisms. As I said, this is dualist; it denies discernibly human material characteristics to something human; the entity looks, expresses itself, and behaves like a pluripotent stem cell; it does not express itself in a way characteristic of a human organism, nor does it have any peculiarly human organismic behavioral characteristics; but it just *might* be informed by a human soul. This is like claiming that a human soul *might* be trapped inside a stone. If we can distinguish between any cell and

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[27]Austriaco, "Are Teratomas Embryos or Non-Embryos?"

[28]Condic and Condic, "Defining Organisms by Organization," 341–342.

a zygote, we should be able to distinguish between an ANT-OAR cell and a zygote.[29]

Questions need to be answered

Critical questions regarding ANT-OAR's fitness for producing pluripotent stem cells in a morally legitimate way need to be answered through initial research using nonhuman animal cells before the technique is ever tried with human cells. The signatories state: "if, but only if, such research establishes beyond a reasonable doubt that oocyte-assisted reprogramming can reliably be used to produce pluripotent stem cells without creating embryos, would we support research on human cells."[30] The presence of Nanog and similarly acting transcription factors in oocytes and zygotes will need to be ruled out. The incompatibility of their expression with embryonic existence will need to be conclusively established. Present evidence demonstrates that such factors maintain the pluripotency of a stem cell by preventing cell differentiation; are we sure their forced expression will also prevent cell dedifferentiation? Another question is, if oocyte cytoplasm is potent enough to reprogram a genome back to a state of totipotency, is it possible that it will also reprogram the altered gene for Nanog expression? This problem may be obviated by employing techniques for forcing gene expression that circumvent the "reprogramming" mechanisms used by oocytes (e.g., forcing RNA expression—the oocyte does not "reprogram" RNA).

One criticism maintains that the reliability of the method used for detecting Nanog is not sufficient to establish moral certitude that the entity created through ANT-OAR is not an embryo: "the *lack of detection* of Nanog in the zygote does not mean that it is not present. Thus the biological underpinning of the OAR hypothesis, namely that the zygote differs from the morula or ICM cells of the blastocyst because it lacks Nanog, cannot be proven with moral

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[29]I am indebted to Maureen Condic for several of the ideas set forth in the preceding two paragraphs.

[30]"Production of Pluripotent Stem Cells by Oocyte-Assisted Reprogramming: Joint Statement with Signatories," *The National Catholic Bioethics Quarterly* 5, no. 3 (Autumn 2005): 579.

certainty."[31] This criticism raises a general question worth asking. Can any scientific protocol be developed that delivers results precise and consistent enough to establish beyond a reasonable doubt that the entity created through ANT-OAR is or is not a human embryo? This question brings us back to the fundamental doubt as to whether science is capable of apprehending the difference between different types of cells. I called the doubt "irrational" since its affirmation implies a denial that science, and by implication the reasoning that derives from sensible observation, can know things with certitude. Although the methodological exactitude of any proof will be limited by the inherent epistemological constraints imposed by the subject matter, and in the case of the scientific method we operate in the domain, not of doubtless certitude as in the domain of divine Revelation, but of statistical certitude in which doubt is never ruled out; nevertheless, it is possible to have certitude beyond a *reasonable* doubt (i.e., *moral certitude*) that the entity created through ANT-OAR is not an embryo. Reasonable doubt is expelled through a process of rigorous material and temporal analysis of the product of the technique. If there is sufficient evidence in animal experimentation to rule out a reasonable doubt that an embryo comes into existence through ANT-OAR, then we proceed to human cell experimentation.

Another related question might be asked: having established that the expression of a desired transcription factor or factors is categorically incompatible with embryonic existence, what is the possibility that in testing for the expression of that transcription factor the method will deliver false positives? This too will need to be addressed during experimentation using nonhuman animal cells. Rigorously testing the products of ANT-OAR will enable us to reliably establish the probability of methodological test failure. If failure rates are statistically negligible, and testing otherwise consistently establishes that the entity produced from ANT-OAR is not an embryo but a pluripotent cell; and the firm intention is to protect the value of human life by *never* producing a human organism; then it may be reasonable to proceed with testing in human cells knowing that a very remote possibility exists that an embryo may result; that

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[31]Women for Faith and Family, "Is Oocyte Assisted Reprogramming (OAR) A Moral Procedure To Retrieve Embryonic Stem Cells?" (15 August 2005, updated 22 September 2005), available at www.wf-f.org/OAR_StemCells.html.

possibility is accepted as an unwanted and unintended side effect of an otherwise morally justifiable act. By analogy, women are sometimes prescribed estrogen pills for the regulation of the menstrual cycle. One activity of orally administered estrogen can be to render a woman's uterine lining inhospitable to a nidating embryo, in the rare instance of a breakthrough ovulation and subsequent fertilization. Knowing this, many Catholic moral theologians agree that for serious reasons the choice of a woman, even a sexually active married woman, to take estrogen pills for purposes of cycle regulation can be legitimate, if a contraceptive intent is excluded. □

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