

Altered Nuclear Reprogramming and Efficient Causality

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ABSTRACT

This essay replies to the claim that the ANT-OAR procedure creates disabled human embryos. It focuses upon the chief locus of disagreement between defenders and opponents, which is the identity of the product of the procedure immediately after nuclear transfer and before and during nuclear reprogramming. Whereas opponents believe that the biological entity that carries out the nuclear reprogramming is a human embryo, this essay argues that such a conclusion is scientifically and philosophically untenable. It argues rather that the efficient cause of nuclear reprogramming is an unnatural ooplast-somatic cell hybrid, a biological construct not found in nature, whose active bodily potencies never exceed those of the vegetative order. Because a principal capacity of the cell at its origin is to convert itself, through a process of nuclear reprogramming, into a stem cell, it is reasonable to consider the product of nuclear transfer before and during reprogramming a stem cell.

DOES ALTERED NUCLEAR TRANSFER (ANT) result in the creation of disabled human embryos? Presently this is only a theoretical question since the procedure to my knowledge has not been tested using human cells.¹ Catholic defenders of the procedure oppose ANT

¹ It has been tested using mouse model experiments, and the principle was proved that fully functional pluripotent stem cells could be procured from cellular products in which the *Cdx2* gene was silenced prior to nuclear transfer. See the work of A. Meissner and R. Jaenisch, "Generation of Nuclear-Transfer-Derived Pluripotent ES Cells from Cloned *Cdx2*-Deficient Blastomeres," *Nature* 439 (2006): 212-21. The authors refer to the product of the experiments as blastocysts and in early press statements as embryos. When pressed on the question of the status of the product at a June 6, 2006 Capital Hill News conference, Jaenisch asserted that the product in his judgment was not an embryo, but because of scientific convention he had referred to it as such. He also spoke to a Senate subcommittee on this matter: "Because the ANT product lacks essential properties of the fertilized embryo, it is not justified to call it an 'embryo'." "Testimony of Rudolf Jaenisch, M.D., Hearing on 'An Alternative Method for

experiments using human cells until extensive study using non-human primate cells provides morally conclusive evidence that the procedure never produces an embryo. Some opponents doubt whether empirical evidence alone will ever be able to substantiate the non-embryonic nature of the product of the procedure.² I have disagreed elsewhere with this and have argued that conscientious scientific method aimed at determining the cell type produced by ANT can arrive at true conclusions.³ To argue otherwise in my judgment is to succumb to rational skepticism. It also is implicitly to deny Aquinas's hylomorphic principle that a thing's nature is revealed in what it does, i.e., in its acts (*agere sequitur esse*).⁴

Obtaining Embryonic Stem Cells,' Comm. on Appropriations, Subc. of Labor, Health & Human Services, Education," U.S. Senate Oct. 19, 2005.

² This is the view of David L. Schindler. See his essay "A Response to the Joint Statement, Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming," *Communio: International Catholic Review* 32/2 (Summer 2005): 369-80, esp. p. 375.

³ E. Christian Brugger, "ANT-OAR: A Morally Acceptable Means for Deriving Pluripotent Stem Cells. A Reply to Criticisms," *Communio: International Catholic Review* 32/4 (Winter 2005): 753-69, esp. pp. 764-65.

⁴ Thomas never formulates the maxim in precisely those three words, but he affirms the basic proposition in many places (e.g., see *Summa contra gentiles* I.43.2; II.7.3,5; III.113.1; *Summa theologiae* I.19.2c, 105.5c; *De Potentia* 2.1c). In an essay within this volume Dolores Meehan claims that the maxim as used by defenders of ANT implies more than the scholastic meaning that a thing's actions are determined by its being; defenders, she says, understand the maxim in the imperative mode: act *must* follow being; it follows, she concludes, that defenders must be implicitly committed to a convertibility of subject and predicate: not only does act follow being but being follows act. She references no sources for her assertions; given the obscurity of their formulations, their meaning is uncertain. If by imperative she means that defenders hold the maxim to be a normative proposition about the ontological order, then she is correct. In this case there is no recourse to imperative mode but only to a normative predication in the indicative mode: a thing's acts are always determined by its nature. As for the convertibility of subject and predicate, she seems to have confused the ontological with the epistemological orders. At the ontological level, actualizations are determined by potentialities; we can only do as our natures are capable of doing. But at the epistemological level, we can only come to *understand* the nature of a thing by observing what it can do (its acts). Aquinas understands *agere* to include observable operations that can be empirically identified and lead an

My intention for this essay is to defend ANT against the criticism that we can know in advance—so ANT critics assert—that the procedure creates or presumptively creates disabled human embryos. I will do this by focusing upon what I see to be the locus of disagreement between defenders and opponents of ANT. The disagreement is over the nature of the product of nuclear transfer just before and during nuclear reprogramming. After an altered nucleus is transferred into an enucleated oocyte, a process begins where the somatic cell nucleus undergoes epigenetic reprogramming. Opponents of ANT argue that the cellular entity that performs the reprogramming of the somatic cell nucleus is the embryo itself. Defenders argue that the entity cannot be an embryo until the nucleus achieves an epigenetic state of totipotency. Prior to achieving the genetic profile of totipotency, it is both scientifically and philosophically reasonable to conclude that the complex of chemical constituents in the oocyte cytoplasm and not an embryo is the efficient cause of the nuclear reprogramming. I will demonstrate how the position defended by critics of ANT entails errors in both scientific and philosophical reasoning.

Although I believe my argument can be applied to different types of ANT, for purposes of this essay I focus on the type called oocyte assisted reprogramming (ANT-OAR), since it has been criticized most frequently in the literature. ANT-OAR proposes to use somatic cell nuclear transfer (SCNT) to bring into existence a cell whose genetic and epigenetic profile is *ab initio* that of a pluripotent stem cell. In standard SCNT the highly specified epigenetic state of the transferred nucleus is reprogrammed by the oocyte cytoplasm to the state of totipotency. Totipotency is the operational genetic and epigenetic profile characteristic of an embryo and a defining quality of the embryo's corporeal potentialities.

Every living cell possesses a set of defining corporeal potentialities. This set of capacities reveals the bodily identity of the cell. In one case it corresponds to the identity of a liver cell, in another to a skin cell, and still another to a cardiac cell. It need hardly be said that if the genetic profile is that of a liver cell, if its capacities are defining of the possible actualizations of a liver cell, if it could never of itself do what a cardiac or skin cell does, then that cell is a liver cell and not a cardiac or a skin cell. If the

observer to arrive inductively at the nature of the thing being observed.

epigenetic profile is totipotency, then the cell possesses the corporeal capacity (or network of capacities) to carry out self-directed, organized development towards species maturity, differentiating all the requisite tissue types and proportionally self-integrating those tissues into its increasingly complex body. Such a cell is the executive of its own corporeal development. If at its coming into existence the developmental potentiality—the set of potential bodily actualizations made possible by its distinctive epigenetic profile—includes the organs through which a minimal rational act could be carried out, the cell has the genetic profile of a human organism, of an embryo.

In standard SCNT, the epigenetic profile of the somatic cell nucleus is reset to a state of totipotency. If totipotency is achieved, the cell with the reset nucleus is, we may presume, a new whole organism at its earliest stage of development, an embryo. Not every transferred nucleus will be successfully reset to a totipotent state. If the nucleus never achieves the state, then the corresponding cell never possesses the corporeal capacities necessary to define it as a whole human organism. If it does not possess the capacities, it does not possess the nature defining of those capacities. So, if the nuclear profile of a cell never achieves totipotency, that cell is never a whole self-organizing biological entity of the species *Homo Sapiens*. It does not possess of itself the capacity to develop its body to a sufficient degree for the actualization of a rational act. The cell is not zygotic in kind.

ANT-OAR proposes genetic manipulations to the somatic cell nucleus *before* transfer into the enucleated oocyte. These manipulations aim at determining the genetic profile of the transferred nucleus in two ways. The first is negative insofar as they exclude the expression of factors that are biologically necessary for the nucleus to achieve a totipotent profile during reprogramming. The second is positive insofar as they express certain factors that positively define pluripotent stem cells but are never expressed in embryos. The alterations of the genetic profile introduced by these manipulations are unaffected by the reprogramming capacities of the oocyte cytoplasm. Upon nuclear transfer, the cytoplasmic constituents reset the nuclear profile of the altered nucleus to a state of pluripotency, and the resultant cell is essentially a pluripotent stem cell.

I said above that every cell in the body possesses a set of defining corporeal potentialities that define the actualized nature (i.e., the identity)

of the cell. In a human embryo these bodily capacities are animated and actualized by a rational soul. But that soul cannot inform a body whose *per se* biological constitution excludes it (i.e., the soul) from expressing its defining actualizations. Both Aristotle and Aquinas affirm the truth that the rational soul is the actualization of a natural body capable of possessing human life.⁵ A body is capable of possessing human life if it possesses of itself the corporeal requisites through which (or in conjunction with which) the soul can carry out its properly human powers. The five animating powers of the rational soul are vegetative, sensitive, appetitive, locomotive, and intellectual.⁶ Each of these powers depends on some minimal degree of bodily development for its operation. The vegetative powers require only a living body of some sort. So, a rational soul could not inform a non-living body. The sensitive, appetitive, and locomotive powers require a living body with a minimally developed perceptual apparatus including both brain and sensory neurological development. A natural body that excluded *per se* the potentiality for such development could not be informed by a rational soul. Finally, the intellectual powers require the development of a fairly sophisticated nervous system that culminates with whole brain development in conjunction with which minimal rational acts might be carried out.⁷ If a natural body does not possess of itself the developmental potentiality to actualize an adequately developed brain, that body would be *inepta materia* for being substantially informed by a rational soul.⁸

⁵ ST I.77.1c; Aristotle, *De Anima* II.1.412a 20-21.

⁶ ST I.78.1c.

⁷ I do not intend here to engage the quantitative question regarding how much brain development is adequate. The principle is clear that some brain development is necessary for rational acts to be exercised.

⁸ This is not to say that intellectual acts are acts of the brain. In Aquinas's account, they are not acts of any corporeal organ but rather of the immaterial soul alone. Aquinas posits the immaterial powers of active and possible intellects in the process of understanding. The active intellect (ST I.79.3-4) he calls the faculty of illumination and abstraction. The power goes to work on representations of sensible images stored in the sense faculties in order to make those images intelligible (i.e., capable of being understood). Sensible objects of knowledge are necessarily material; to be understood they need to be made immaterial. Cognition

The principle is crystal clear in Aquinas: *whatever is received into something is received according to the mode of the recipient.*⁹ If therefore the recipient excludes *ab initio* the possibility for the carrying out of an act of rationality, *then that recipient could not receive the substantial form of a rational soul.* Only a totipotent epigenetic profile possesses *ab initio* the possibility for a developmental trajectory the terminus of which is a body developed enough for the rational soul to carry out rational acts. This does not mean that the cell's history must include the actual development of those organs. There are many factors that can impede the actualization of naturally indicated capacities. But if they were never

begins with sensible images, which have all the characteristics of material objects in sensible form. They are surrounded by all the sensible conditions of materiality: particularity, spatiality, and temporality; represented with shape, size, and distance, and in terms of color, sound, flavor, odor, and feel; all these things need to be stripped away for universal concepts to emerge and understanding to be actualized. Something is needed then to reduce the image from being only potentially intelligible to being actually intelligible. This is performed by what Aquinas calls the agent intellect: the power by which intellect abstracts the "what" (that is, the essence) of the thing from the sensed material conditions in which it is embedded. In the language of Thomism, we say the agent intellect abstracts intelligible forms from sensible forms. Since it actualizes intelligibility in sensible things (or makes *intelligibles* in act), the agent intellect is the efficient cause of all things that are actually intelligible (SCG II.78.4). The sensible images are brought before the agent intellect by the internal senses of imagination and memory in the form of *phantasms* (actual images of material things no longer present). This means that in the process of knowing the intellect *always* operates in relation to phantasms: all knowing requires a preliminary act of abstraction that itself requires a preliminary act of sensation. Consequently sensation is a condition for human knowing. Thus we get the scholastic maxims: *nothing is in the intellect that was not first in the senses.* It follows that the human person in order to actualize its most godlike (immaterial) perfections *needs a body*, because without a body there is no sensation. The body therefore is necessary for the actualization of *all* the powers of the soul (although not all actualizations are reducible to the actualization of body). The role of the possible intellect is to receive the intelligible form from the agent intellect and to bring forth from it understanding in the form of an idea. See my defense of Aquinas's account of the immateriality of the intellect in "Aquinas on the Immateriality of Intellect: A Non-Materialist Reply to Materialist Objections," *National Catholic Bioethics Quarterly*, forthcoming.

⁹ ST I.75.5c.

indicated in a natural body in the first place, then the body was never capable of possessing *human* life, was never capable of receiving the substantial form of a rational soul, and thus was never an embryo.

This conclusion has been steadfastly rejected by critics of ANT-OAR. In the criticisms raised elsewhere in this volume, the names of David L. Schindler and Adrian Walker continue to resurface as scholarly sources.¹⁰ This is unsurprising since the two are the most dedicated critics. I have replied elsewhere to Schindler by stating my reasons for rejecting his conclusions.¹¹ My principal objection was Schindler's contention that the immediate product of the nuclear transfer is an embryo. How could it be an embryo without an embryonic epigenetic profile? Does he mean to say that the ooplast and differentiated nucleus during reprogramming are *already* an embryo? Walker, replying to my essay, makes his reply to this question explicit. He argues that in order for the oocyte cytoplasm to reprogram the nucleus, the enucleated oocyte must first "fuse" with the somatic cell nucleus, thereby producing a "new cell." This "new cell," he asserts, "is the *suppositum*, the 'ontological subject,' both of the repro-

¹⁰ Schindler has used the journal for which he is editor to publish a large number of his and Walker's criticisms as well as replies by defenders of ANT. For Schindler's articles see David L. Schindler, "A Response to the Joint Statement 'Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming,'" *Communio: International Catholic Review* 32/2 (Summer 2005): 369-80, "Veritatis Splendor and the Foundations of Bioethics: Notes towards an Assessment of Altered Nuclear Transfer and Embryonic (Pluripotent) Stem Cell Research," *Communio: International Catholic Review* 32/1 (Spring 2005): 195-201; "Agere sequitur esse: What does It Mean? A Reply to Father Austriaco," *Communio: International Catholic Review* 32/4 (Winter 2005): 795-824; for Walker's contribution, see Adrian J. Walker, "The Primacy of the Organism: Response to Nicanor Austriaco" and "A Way around the Cloning Objection against ANT? A Brief Response to the Joint Statement on the Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming," both in *Communio: International Catholic Review* 32/1 (Spring 2005): 177-87 and 188-94 respectively, "Reasonable Doubts. A Reply to E. Christian Brugger" and "Who Are the Real Aristotelians? A Reply to Edward J. Furton," both in *Communio: International Catholic Review* 32/4 (Winter 2005): 770-83 and 784-94.

¹¹ Brugger, "ANT-OAR: A Morally Acceptable Means for Deriving Pluripotent Stem Cells. A Reply to Criticisms," *Communio: International Catholic Review* 32/4 (Winter 2005): 753-69.

gramming process and of whatever epigenetic states that process eventually results in.”¹² He continues: “The simplest interpretation of the facts is that a new human being has come into existence and is running itself through the epigenetic reprogramming process.”¹³ His argument rests on the contention that a new cell comes into existence before reprogramming, a point that he says has “huge bearing on the argument.”¹⁴ And Walker is confident that this new cell is “a new human being.” What grounds Walker’s confidence that the new cell is an embryo? His belief derives from the premise, affirmed by Schindler, that the joining of an ooplast and a somatic cell nucleus is *per se* defining material for a human life to come into existence whatever the epigenetic profile of the nucleus.¹⁵ When the two “fuse,” it “mimics conception.”

We can accept Walker’s view that a new cell begins immediately after transfer and before reprogramming and still strenuously deny that the product is always presumptively a human embryo.¹⁶ It is not an embryo unless it possesses or is capable of itself of achieving an embryonic nature. That nature is not merely a function of a diploid nucleus in an ooplast body. Those constituents must have in addition the active capacity to carry out the operations of an embryo, namely, to orchestrate bodily development towards species maturity. If a cell has of itself this capacity, it has the nature of an embryo and so *is* an embryo. If it does not and never will have the capacity to do what an embryo does, it does not have

¹² Walker, *A Reply to E. Christian Brugger*, p. 774.

¹³ *Ibid.*, p. 775.

¹⁴ *Ibid.*, p. 775 n11.

¹⁵ *Ibid.*, 776; cf. Schindler, *A Response to the Joint Statement*, p. 371.

¹⁶ Another possibility is to reject Walker’s hypothesis that a new cell comes into existence before reprogramming and to say rather the beginning of a new cell waits until reprogramming is complete. The efficient cause of the nuclear reprogramming would then not be the cell itself but rather the complex of chemical factors in the egg cytoplasm. The reprogramming system would not be a new living cell, but an ooplast carrying out a chemical operation on a somatic cell nucleus. When the operation is complete, the system may then take on the identity of a new cell. This seemed to me more likely at first, but upon further reflection, I am inclined to accept Walker’s claim that a new cell begins after transfer. We disagree, however, on the identity of that cell.

the nature of an embryo and so is not an embryo. To do what an embryo does, a cell must have more than a diploid nucleus in an ooplast body, for dermoid cysts, hydatidiform moles and other species of teratoma tumors can begin with this type of body. To be consistent, Schindler and Walker would need to maintain that each and every one of these began as an embryo. They would also need to maintain that every product of natural conception is in principle an embryo, no matter what the disorders that characterize the epigenetic profile. Further, they would be committed to holding that every parthenogenically activated oocyte is an embryo since oocytes before fertilization possess diploid nuclei. Although it is possible that some partial moles and other kinds of gamete-derived tumors begin as embryos, it is impossible for any one of them to be an embryo if it never possesses an embryonic epigenetic profile.

The intention in using ANT-OAR is to create a cell that does not begin with a totipotent nucleus and never achieves a state of totipotency. The product is intentionally made incapable of achieving such a state. This means that the “new cell” *never* possesses of itself the active corporeal potency to develop a body that is organized enough for the soul to carry out its principal operations through or in conjunction with it. It is a metaphysical principle that if a thing lacks certain active potencies, it lacks the nature that defines those potencies. If ANT-OAR therefore works according to principle, the cellular product that it creates will lack a nature capable of developing a body that could ever actualize acts of perception, appetite and locomotion and thereby serve as the necessary organic counterpart to acts of rationality. It *fails* to meet the definition of a natural body capable of possessing human life.¹⁷

What kind of cell is it then, and what are its defining capacities during reprogramming? The new cell is an unnatural ooplast-somatic cell hybrid, a biological construct not found in nature. Its active bodily potencies could not exceed those determined by the genetic and epigenetic profile and biochemical powers of its own organic constitution. Responding to developmental signals, the new cell is capable of actively initiating and orchestrating alterations in its own properties during a process of differentiation and maturation—effectively converting itself from its hybrid

¹⁷ ST I.77.1c; Aristotle, *De Anima* II.1.412a 20-21.

type into a pluripotent stem cell. So, we can say that one of its capacities is to convert itself into a stem cell. Because the cell at its origin has this active capacity, it is reasonable to consider it at its origin a stem cell.

This is why standard SCNT is so problematic. The teleological trajectory of the new cell that begins upon nuclear transfer includes actualizing the body of a zygote. The activated system from its *terminus a quo* moves inexorably to a human organismic conclusion, that is, its *terminus ad quem* is an embryo. It is therefore reasonable to treat the activated system from the beginning as an embryo. But the ANT-OAR derived cell begins its life actively prevented from ever actualizing the body of a zygote. At no time, then, do its capacities include the development of a body through which and in conjunction with which perception and rational acts could be carried out. Lacking such capacities, *the cell lacks the actualized nature from which and only from which those capacities could arise*. The capacities of the new cell could never be said to exceed those of the vegetative order. The body from *terminus a quo* to *terminus ad quem* would constitute *inepta materia* for being substantially informed by a rational soul.

I have argued that no rational soul can be the substantial form of a material body that lacks the active potencies defining of human nature. This means that no single cell without a state of totipotency can be an embryo. If we accept Walker's claim that the ooplast fuses with the nucleus before reprogramming, it follows that the new cell "running itself through the epigenetic reprogramming process"¹⁸ is not a human embryo since it is *per se* incapable of possessing more than a vegetative soul.

I said that I would demonstrate how the position defended by critics of ANT-OAR entails errors in both scientific and philosophical reasoning. The philosophical error is asserting that humanness can inform a natural body incapable of itself of actualizing defining capacities of a human being. The scientific error is judging that a cell that was never capable of achieving a state of totipotency can be or can ever have been a human embryo.¹⁹

¹⁸ Walker, *A Reply to E. Christian Brugger*, p. 775.

¹⁹ I would like to thank Dr. William Hurlbut and Dr. Maureen Condic for valuable comments in preparing this essay.