Essays

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Are Teratomas Embryos or Non-embryos?

A Criterion for Oocyte-Assisted Reprogramming

Rev. Nicanor Pier Giorgio Austriaco, O.P.

Recent advances in our ability to manipulate oocytes and to transform them into embryo-like entities have reinvigorated the debate on the ontological status of hydatidiform moles and parthenotes. The hydatidiform mole is an embryo-like entity that is generated by an abnormal fertilization event. In human beings, a mole develops into a disorganized mass that can become a tumor. In the past, noted Catholic moralists argued that similar tumors, called teratomas (which usually derive from germ cells in the ovary), are not embryos, since these so-called embryos are substantially defective from the outset.[1] More recently, however, other Catholic bioethicists have suggested that the human mole *may once have been* a human embryo. For

[1] Germain Grisez writes: "Many biologists and physicians going by appearance have believed these tumors to be embryos whose development had gone astray. But authoritative and recent examination of the question has led to the conclusion that these growths are simply tumors—rather disorganized but somewhat differentiating bundles of material deriving from an individual's own body. Teratomas are not malformed embryos." See his *Abortion: The Myths, the Realities, and the Arguments* (New York: Corpus Books, 1970), 28. Benedict Ashley, O.P., and Albert S. Moraczewski, O.P., agree with Grisez: "Bedate and Cefalo argue from existence of hydatidiform moles and teratomas that genetic individuation is not sufficient since these entities arise from zygotes. This argument, however, seems definitively refuted since it is now known that the so-called 'zygote' in question is radically defective from the outset." See their "Is the Biological Subject of Human Rights Present from Conception?" in *The Fetal Tissue Issue: Medical and Ethical Aspects*, ed. Peter J. Cataldo and Albert S. Moraczewski, O.P. (Braintree, MA: The Pope John XXIII Medical-Ethics Research and Education Center, 1994), 37–38.

instance, Fr. Tadeusz Pacholczyk has argued that as moles develop and become highly disorganized, "such embryos may in certain instances pass through an initial stage where they are normal or nearly normal human organisms."[2] A similar debate has arisen over the ontological status of parthenotes, embryo-like entities that are generated when an oocyte is activated to begin dividing in the absence of sperm. Again, in human beings, parthenotes, like moles, develop into tumors. So, are moles, parthenotes, and other tumor-forming entities embryos or non-embryos?

In this brief essay, I argue that the ontological status of moles, parthenotes, and other embryo-like entities that develop into tumors will depend on two distinctions, the distinction between an active and a passive potential, and the distinction between a whole and a part. I propose that an embryo-like entity that has an active potential to wholly become a tumor (such entities would include complete hydatidiform moles and parthenotes) is a non-embryo, while an entity that has an active potential to become a tumor only in part (such entities would include partial hydatidiform moles) is an embryo, albeit a disabled one. Finally, in light of this analysis, I will suggest that tumor formation can be used as a test to distinguish between embryos and non-embryos in protocols involving altered nuclear transfer (ANT) or oocyte-assisted reprogramming (OAR).

Hydatidiform Moles and Parthenotes: Biological Notes

There are two kinds of hydatidiform moles.[3] A partial hydatidiform mole forms when two sperm fertilize a normal oocyte, resulting in a conceptus with sixty-nine chromosomes. The presence of three copies of each chromosome (triploidy) leads to death of the conceptus early in the pregnancy or, more rarely, in late-term loss of the abnormal fetus. Partial moles are characterized by disorganized placental and fetal growth. However, and this is important, the partial hydatidiform mole often presents itself as a tumor associated with a recognizable fetus.

In contrast, a complete hydatidiform mole forms when an enucleated oocyte is fertilized by two sperm, or by one haploid sperm which then duplicates its chromosomes. Thus, the product of conception has forty-six chromosomes—the normal number—but all of them are derived from the father. The resulting mass is made up solely of tissue derived from one type of embryonic cell, the trophectoderm. In other words, the tumor is made up of placental tissue exclusively, and no fetal tissue is present. Complete hydatidiform moles always develop into tumors.

Finally, a parthenote is an oocyte that has been activated to begin to divide and to develop in the absence of sperm.[4] There are many experimental procedures (mechanical, electrical, and chemical) which can artificially activate the mammalian oo-

[2] Tadeusz Pacholczyk, "The Substantive Issues Raised by Altered Nuclear Transfer," letter, *National Catholic Bioethics Quarterly* 5.1 (Spring 2005): 18.

[3] For a review, see R. C. Bentley, "Pathology of Gestational Trophoblastic Disease," *Clinical Obstetrics and Gynecology* 46.3 (September 2003): 513–522.

[4] For a review, see N. Rougier and Z. Werb, "Minireview: Parthenogenesis in Mammals," *Molecular Reproduction and Development* 59.4 (August 2001): 468–474.

cyte in this way. Such activated human oocytes have been able to develop in vitro to the five-day, one-hundred-cell blastocyst stage in a manner apparently indistinguishable at the gross morphological level from the early development of normal human embryos.[5] In vivo, there is evidence that human parthenotes develop into ovarian tumors.[6] These observations may not be contradictory, since a report that studied the development of mouse parthenotes in vitro from a certain mouse species suggests that in this species, activated oocytes develop to what appears to be a blastocyst stage before becoming tumors.[7]

Hydatidiform Moles and Parthenotes: Philosophical Notes

So, are hydatidiform moles and parthenotes disabled embryos or non-embryos? First, there is good reason to think that a partial hydatidiform mole is an abnormal human embryo, not unlike certain children who are born with a triploid genome.[8]

With partial hydatidiform moles, the tumor is often associated with a grossly abnormal but recognizable human fetus. The presence of the fetus suggests that with a partial mole, the extra copy of each gene distorts the development of the embryo. One manifestation of this abnormality is the development of a tumor. Or to put it another way, with a partial mole, an already-abnormal embryo develops cancer.

On the other hand, there is also good reason to think that a complete hydatidiform mole is not an embryo. In brief, a complete mole has a functionally incomplete genome. It lacks certain molecules ab initio, and this radically changes its developmental trajectory. Instead of becoming an organized structure of differentiated cells and tissues, a complete mole develops into a tumor composed of one cell type, which is placental.

Recall that the complete mole inherits all of its forty-six chromosomes from the father. This is significant, because in mammalian organisms, a small number of genes are inactive if they are inherited from one particular parent and not from the other.

[5] N. Rogers et al., "Phospholipase C-zeta Causes Ca2+ Oscillations and Parthenogenetic Activation of Human Oocytes," *Reproduction* 128.6 (December 2004): 697–702.

[6] F. Oliveira et al., "Evidence of Parthenogenetic Origin of Ovarian Teratoma: Case Report," *Human Reproduction* 19.8 (August 2004): 1867–1870. Also see G. H. Lee et al., "Genetic Dissection of Susceptibility to Murine Ovarian Teratomas That Originate from Parthenogenetic Oocytes," *Cancer Research* 57.4 (February 15, 1997): 590–593.

[7] Y. Hirao and J. J. Eppig, "Parthenogenetic Development of *Mos*-Deficient Mouse Oocytes," *Molecular Reproduction and Development* 48.3 (November 1997): 391–396. This study focused on genetically modified oocytes lacking the *Mos* gene. However, there are no data to suggest that the overall behavior of these parthenotes would have been any different from the behavior of parthenotes containing *Mos*.

[8] Although there are reports of children born with triploid genomes, these children do not survive beyond 10.5 months. For one case study, see J. Sherard et al., "Long Survival in a 69,XXY Triploid Male," *American Journal of Medical Genetics* 25.2 (October 1986): 307–312. For a detailed description of triploidy, see the informative Web site "Triploidy," by the Texas Department of State Health Services, at http://www.dshs.state.tx.us/birthdefects/risk/risk24-triploidy.shtm.

This is the phenomenon called genomic imprinting.[9] For example, the *Igf2* gene encoding insulin-like growth factor type-2 is expressed if it is inherited from the father, but it is imprinted, i.e., rendered silent, if it is inherited from the mother.[10] In contrast, the *Igf2r* gene encoding the receptor for insulin-like growth factor type-2 is expressed if it is inherited from the mother, but it is imprinted if it is inherited from the father.[11] Thus, in effect, a complete mole lacks expression of all the genes that are active only if they are inherited from the mother. Functionally, therefore, a complete mole has an incomplete genome. It is a living system that lacks molecules that are absolutely associated with a human embryo.[12]

Furthermore, because of the absence of these molecules that are only present when the genes that encode them are inherited from the mother, the complete hydatidiform mole cannot progress through the developmental stages associated with early human embryogenesis. Instead, it simply grows into a tumor, which is often composed of only one or, at most, a few cell types, all of placental origin. There is no sign of fetal tissue and no sign of cellular specialization. Significantly, there is also evidence from mice that suggests that the imprinting of certain genes has an effect on the development of the whole embryo from the very beginning, at the two-cell stage.[13] Together, the data show that the complete hydatidiform mole cannot be and is not any kind of unified organism ab initio. In other words, from the beginning, it is not an individual member of a particular biological species distinguished by a species-specific developmental trajectory that consists of a sequential and ordered appearance of differentiated cells and tissues. Therefore, it cannot be an embryo.

Challenging this conclusion, Fr. Pacholczyk has suggested that as moles develop and become highly disorganized, they may pass through an initial stage of normality, in which they are normal or nearly normal human organisms that then become subject to disorganizing forces. He writes:

> Nevertheless, the conceptual question remains whether even such an aberrantly growing entity like a [complete hydatidiform mole] may not initially pass

[9] For a review of genomic imprinting, see M. Wrzeska and B. Rejduch, "Genomic Imprinting in Mammals," *Journal of Applied Genetics* 45.4 (2004): 427–433.

[10] For details, see R. Ohlsson, "Loss of IGF2 Imprinting: Mechanisms and Consequences," *Novartis Foundation Symposium* 262 (2004): 108–121. Also see R. Ohlsson et al., "IGF2 is Parentally Imprinted during Human Embryogenesis and in the Beckwith-Wiedemann Syndrome," *Nature Genetics* 4.1 (May 1993): 94–97.

[11] A. Wutz et al., "Imprinted Expression of the *Igf2r* Gene Depends on an Intronic CpG Island," *Nature* 389.6652 (October 16, 1997): 745–749.

[12] For a description of the systems perspective that is presupposed here, see the following essays: N. P. G. Austriaco, O.P., "Immediate Hominization from the Systems Perspective," *National Catholic Bioethics Quarterly* 4.4 (Winter 2004): 719–738; and N. P. G. Austriaco, O.P., "On Static Eggs and Dynamic Embryos: A Systems Perspective," *National Catholic Bioethics Quarterly* 2.4 (Winter 2002): 659–683.

[13] D. Rappolee et al., "Insulin-like Growth Factor II Acts through an Endogenous Growth Pathway Regulated by Imprinting in Early Mouse Embryos," *Genes & Development* 6.6 (June 1, 1992): 939–952.

> through a brief human organismic stage prior to becoming subject to powerful *dis*-organizing forces (in the form of non-expressed or inappropriately expressed genes) which cause it to fail as an organism.[14]

In other words, according to Fr. Pacholczyk, a complete mole could have been a human embryo that had the potential to become a tumor. But what does this mean exactly? What does it mean to say that a human embryo has the potential to become a tumor?

To respond, we begin by noting that there is a distinction between an active and a passive potential. An active potential is actualized wholly from within. It is indicative of an entity's nature—its ontological status. For example, an acorn has an active potential to become an oak tree. In contrast, a passive potential is actualized from without. It requires the active causal intervention of an external agent in order to be realized. Thus, an acorn only has a passive potential to become a crucifix because it would need the agency of a master craftsman in order to realize this end.

Given this distinction, what does Fr. Pacholczyk mean? Clearly, he cannot mean that a complete mole could have been a human embryo that had an active potential to become a tumor. This would be incoherent. By nature, human embryos do not become tumors. Thus, they cannot have an active potential to become tumors. Fr. Pacholczyk also cannot mean that a complete mole could have been a human embryo that had a passive potential to become a tumor. By definition, a passive potential needs an external agent in order to be realized, and it is clear from his challenge that Fr. Pacholczyk is referring to internal disorganizing forces arising from non-expressed or inappropriately expressed genes.[15] Thus, for Fr. Pacholczyk's proposal to be coherent, he must mean that a complete mole could have been a human embryo in which one part of the whole had an "active" potential to become a tumor.[16] This part then developed into the tumor that radically distorted the overall trajectory of the embryo, eventually killing the embryo.

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[14] Tadeusz Pacholczyk, "The Substantive Issues Raised by Altered Nuclear Transfer," *National Catholic Bioethics Quarterly* 5.1 (Spring 2005): 18.

[15] However, there is evidence that normal mammalian embryos have a *passive* potential for tumor formation. For example, if a normal mammalian embryo is transplanted under the kidney capsule of an athymic mouse, it can develop into a tumor. Here it is likely that the abnormal physiological environment of the kidney capsule kills the embryo by transforming it into a tumor. For technical details, see G. B. Anderson et al., "Development of Bovine and Porcine Embryonic Teratomas in Athymic Mice," *Animal Reproduction Science* 45.3 (December 16, 1996): 231–240.

[16] Properly speaking, since active potentials are manifestations of substantial forms, which are principles of organization, there can be no active potential for tumor formation, a process that involves disorganization rather than organization. Therefore, it is more proper to say that a tumor arises in a human being because of a defect in the *material cause*, which affects a part of the human embryo. To put it another way, a tumor arises because the formal cause, the human soul, is unable to properly realize the potencies in part of the material cause. This defect leads to the abnormal actualization of hidden potencies in the material cause, which manifest themselves as the disordered growth we call a tumor. For this clarification, I am indebted to Professor Michel Bastit of the University de Bourgogne, in Dijon, France.

Given this analysis, we can respond to Fr. Pacholczyk's challenge by asking the following question: In a complete hydatidiform mole, do the genetic defects that distort its developmental trajectory and lead to tumor formation affect the whole mole or only a part of it? If the imprinting or silencing defects affect the whole, then tumor formation is the actualization of an "active" potential that reflects the nature of the mole.[17] On the other hand, if the imprinting defects affect a part of the mole, then tumor formation is simply the distortion of a once-normal embryo. Although to the best of my knowledge no scientific experiments on human embryos have been performed to directly address this question—experiments that would be morally reprehensible—there is scientific evidence from developing mice that suggests that the non-expression of parentally imprinted genes affects the development of the whole embryo and not only a part, even at the two-cell stage.[18] This suggests that tumor formation is a manifestation of the nature of the complete hydatidiform mole. Therefore, a complete mole is not an embryo. In contrast, as already noted above, the evidence from partial moles suggests that tumor formation is a manifestation of a defect in a part, whereby one part of the embryo becomes a tumor in the context of the abnormal development of the fetus. Thus, a partial mole is an embryo, albeit a disabled one.

Finally, it is important to note the parallels between complete hydatidiform moles and parthenotes. Recall that a complete mole is an embryo-like entity that results from an abnormal fertilization event in which an enucleated oocyte is fertilized by two sperm (or one haploid sperm which then becomes diploid). Thus, a complete mole has the normal number of forty-six human chromosomes, but they are all derived from the father. In contrast, a human parthenote results from an abnormal "fertilization" event in which an oocyte has been activated to begin dividing. In the process of activation, the haploid oocyte duplicates its twenty-three chromosomes. Thus, the parthenote too has the normal number of forty-six human chromosomes, but they are all derived from the mother. Not surprisingly, therefore, mammalian parthenotes, like complete moles, have a defective genome. In this case, they lack the expression of all the genes that are active only if they are inherited from the father. Not surprisingly, therefore, our analysis of the ontological status of parthenotes parallels our earlier analysis of the ontological status of complete hydatidiform moles.

For our analysis, the definitive question that arises is the following: Does the absence of gene products that are produced only by genes inherited from the father (because they are maternally imprinted) affect the system dynamics of the whole

[17] As explained in the previous note, there cannot be an *active* potential for tumor formation, properly speaking. In this case (in which the whole is affected), it is more correct to say that the tumor arises because of a defect in the material cause that affects *the entire cell mass.* In other words, the tumor arises because the human soul cannot properly inform the defective matter. This failure of ensoulment leads to the abnormal actualization of hidden potencies, which manifest themselves as tumor growth.

[18] Rappolee et al., "Insulin-like Growth Factor II," 939–952. See also C. Walsh et al., "The Non-Viability of Uniparental Mouse Conceptuses Correlates with the Loss of the Products of Imprinted Genes," *Mechanisms of Development* 46.1 (April 1994): 55–62.

parthenote ab initio, substantially changing it so that the whole parthenote becomes a tumor, or does their absence lead to a defect in only *part* of an embryo, such that the part becomes a tumor which eventually kills the whole?

In response, we return to a key study, mentioned above, that has shown that the absence of both paternally and maternally imprinted genes affects the development of the embryo from the very beginning, at the two-cell stage.[19] The absence of the maternally imprinted (paternally produced) molecules affects the parthenote at the level of the whole, since the scientific evidence suggests that the involved genes regulate the overall number of cells that develop in the blastocyst. In addition, two other studies have demonstrated that the organization of a parthenote differs from the organization of a normal embryo from the very start. One of these studies found that in normal development, when the single-celled mouse zygote divides into two cells, these two cells, called blastomeres, are already not identical. One of the two cells divides ahead of its sister and tends to contribute most of its cellular descendants to the embryo proper, which will develop into the baby's body, whereas the other, later-dividing cell contributes cells predominantly to the extra-embryonic tissue, including the placenta, which will develop into the afterbirth.[20] The other study found, in contrast, that when a single-celled mouse parthenote divides into two cells, these two cells do not behave the way normal blastomeres would behave.[21] The sister cell that first divides does not necessarily contribute its descendants to the embryo proper. This is a small but significant difference in organization that points to the difference between the parthenote and the normal embryo at the very earliest stages of development. In sum, all of these data suggest that the forces that lead to tumor formation are already present at the earliest stages of embryonic development. In other words, the system dynamics of the parthenote as a whole already differs from the system dynamics of the normal embryo, since normal embryos do not become tumors. Like the complete mole, a parthenote is not an embryo.

But what about blastocyst formation? As we noted above, there is evidence that human parthenotes have been able to develop to the blastocyst stage in vitro. If the parthenote is not an embryo, why does it develop at least to the blastocyst stage? There is a ready explanation for this. Numerous studies have shown that the oocyte contains molecules from the mother that can compensate for defects in the embryo's genome. For instance, embryos lacking the gene for E-cadherin, an essential molecule that glues cells together, are able to maintain their integrity until the blastocyst stage because of a small amount of residual E-cadherin from the oocyte. However, when the store of maternally derived E-cadherin is depleted, the embryo's cells

[19] Rappolee et al., "Insulin-like Growth Factor II," 939–952.

[20] For details, see Karolina Piotrowska et al., "Blastomeres Arising from the First Cleavage Division Have Distinguishable Fates in Normal Mouse Development," *Development* 128.19 (October 2001): 3739–3748.

[21] Karolina Piotrowska and Magdalena Zernicka-Goetz, "Early Patterning of the Mouse Embryo—Contributions of Sperm and Egg," *Development* 129.24 (December 2002): 5803–5813.

dissociate and the embryo collapses.[22] This defect is evident at the molecular level from the very beginning, as levels of maternally derived E-cadherin molecules gradually decrease, but the morphological effects take time to manifest themselves. In the same way, it is not surprising that the effects from the absence of the maternally imprinted molecules in the parthenote are not completely manifested until the blastocyst stage. The molecular defect within the parthenote is temporarily masked by the molecules inherited from the mother. This, however, does not detract from the reality that the parthenote, in itself, is a teratoma-forming entity, a non-embryo, from the very beginning.

Tumor-Formation: A Criterion for Successful Oocyte-Assisted Reprogramming

In recent months, several scientists and ethicists have developed a proposal to create pluripotent stem cells without destroying embryos. One proposed strategy, called oocyte-assisted reprogramming, or OAR, is a variant of the strategy of altered nuclear transfer (ANT) first described by William Hurlbut of Stanford University.[23] With OAR, the nucleus of a somatic cell, which has been altered so that it contains molecular determinants uniquely associated with stem cells, is transferred into an enucleated oocyte to create a new cell.[24] Theoretically, because of the genetic alterations to the transferred nucleus, the resulting cell should be a pluripotent stem cell with properties identical to those of embryonic stem cells. The goal of OAR is to use the enucleated oocyte to *directly* transform the transferred nucleus into a pluripotent stem cell, completely skipping any embryonic stages. This should alleviate the concerns of those critics of ANT who have argued that ANT might produce a severely deformed embryo. Nevertheless, some of these critics raise a legitimate question: How would one definitively show that no embryo is ever produced with OAR?

In response, I suggest that tumor formation would be one criterion for successful OAR. One essential element of testing OAR on animals would be to implant an OAR-generated cell, the product of nuclear transfer into the enucleated oocyte, into the uterus of a competent female. If the OAR-generated cell develops into a fetus or even a mature organism, then clearly OAR generates embryos. However, if the OAR-generated cell becomes a tumor, then OAR does not produce embryos, since an embryo considered as a whole entity does not have the active potential to become a tumor. The tumor-forming potential would be present in the OAR-generated cell from the beginning, since the genetic alterations are performed before the creation of

[22] L. Larue et al., "E-cadherin Null Mutant Embryos Fail to Form a Trophectoderm Epithelium," *Proceedings of the National Academy of Sciences USA* 91.17 (August 16, 1994): 8263–8267.

[23] William B. Hurlbut, "Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells," *National Catholic Bioethics Quarterly* 5.1 (Spring 2005): 145–151.

[24] Joint Statement with Signatories, "Production of Pluripotent Stem Cells by Oocyte-Assisted Reprogramming," *National Catholic Bioethics Quarterly* 5.3 (Autumn 2005): 579–583.

the cell. Furthermore, the potential would be a property of the whole, since it would affect the cell and all subsequent cells derived from the initial cell. Given these two characteristics, this OAR-generated entity could not be an embryo.

A Response to David Schindler's Critique of OAR

In a recent essay, Professor David L. Schindler has argued that OAR in general, and the experimental test of OAR advocated here in particular, are flawed because they depend on faulty philosophical assumptions. He concludes that tumor formation thus cannot be an adequate test for OAR:

> Given OAR's mechanistic premise—namely, that the nature of the unicellular zygote as such depends on its epigenetic state—the experimentation recommended here will beg, and cannot but beg, a principled answer to the crucial question: namely, whether the entity produced by OAR fails to grow into a mouse because it is a mouse embryo that is gravely defective or because on the contrary it is not a mouse embryo at all. On the other hand: insofar as the recommended experimentation yields its expected results—that is, yields entities that develop into "tumors"—, the experimentation will in fact have certainly confirmed only its original mechanistic premise regarding the nature of an embryo, even though researchers, on the basis of their faulty philosophical assumptions, will claim to have demonstrated that OAR produces a non-embryo rather than a gravely defective embryo.[25]

According to Schindler, the fundamental mistake embraced by proponents of OAR is the method's mechanistic premise, quoted above, that the nature of the unicellular zygote as such depends on its epigenetic state. He argues that epigenetics cannot tell us about the ontological status of a cell: "Epigenetics can determine only the phenotypical manifestation of the cell whose identity is at issue, not its (ontological) identity as such."[26]

In response, I suggest that Schindler's argument is self-referentially incoherent. Note that in his essay, Schindler makes numerous references to the human oocyte. He is even able to distinguish an oocyte from a somatic cell. For instance, he writes, "OAR presupposes an actual fusion of an oocyte and a somatic cell nucleus, and thus mimics conception."[27] But given his own argument, how can he do this? How can he distinguish an oocyte from a somatic cell? Biologists can distinguish oocytes and somatic cells only because they have different biological properties or, in Schindler's terminology, different "phenotypical manifestations." Schindler, however, argues that "phenotypical manifestations" cannot reveal ontological identities. Thus, despite the differences in their "phenotypical manifestations," an oocyte and a somatic cell, according to Schindler, may be ontologically identical. If we follow Schindler's logic,

[25] David L. Schindler, "A Response to the Joint Statement, 'Production of Pluripotent Stem Cells by Oocyte Assisted Reprogramming,'" *Communio* 32.2 (Summer 2005), http://www.communio-icr.com/ant.htm.

[26] Ibid.

[27] Ibid.

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.[28] Again, we could never be sure, since "phenotypical manifestations" cannot reveal ontological identities. Therefore, if we take Schindler's argument to its logical conclusion, we could never legitimately do any experiments with human cells, since each cell, despite its epigenetic state or "phenotypical manifestation," could be an organism. This is obviously unreasonable.

Instead, I suggest that to all reasonable individuals, it is obvious that there is an ontological difference between a skin cell and a liver cell cultured in a petri dish, even between genetically identical skin and liver cells taken from the same person. They are different kinds of cells. We know this because they manifest different biological properties and morphological markers. This is not an argument derived from a flawed mechanistic philosophy. This is an argument grounded in the Aristotelian-Thomistic axiom, *agitur sequitur esse*, act follows from being. To put it another way, the skin cell and the liver cell are different ontologically because they are organized and behave differently. Thus, contrary to Schindler's argument, we can reasonably and with certitude conclude that an OAR-generated entity that becomes a tumor is ontologically different from an embryo, because its different organization and behavior shows that it has a different nature. Again, *agitur sequitur esse*.

[28] Note that a single-cell human zygote is genetically identical to most of the cells that will make up the mature organism later in human development. Therefore, for the most part, the difference between the zygote and a typical adult somatic cell can be traced to epigenetic rather than genetic differences.