ANT-OAR: Is Its Underlying Philosophy of Biology Sound?

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"The same problems that arose with regard to ANT apply equally to ANT–OAR."

The ongoing debate about ANT-OAR may turn out to be fruitful not only for resolving this particular issue of bioethics, but also for reflecting on the fundamental questions concerning the beginnings of human life.

In this regard, I think that insufficient attention has been given to the view of Systems Biology that underlies the original proposal for ANT as presented by William Hurlbut (I will call this original proposal ANT-1).[1] This form of ANT consists, broadly, in nuclear transfer, but with the following modification: the *Cdx2* gene (or some analogous gene) of the adult cell nucleus is switched off before the transfer. The effect of this modification is that after a few cell divisions the trophectoderm fails to form properly and the entity is incapable of developing further in a structured way.

ANT-OAR is another form of ANT. In normal SCNT, after the donor nucleus is introduced into the enucleated egg, the somatic

[1]For a description of the procedure, see William B. Hurlbut, "Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells," *The National Catholic Bioethics Quarterly* (=*NCBQ*) 5 (2005): 145–151.

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cell nucleus undergoes a process of reprogramming. The nucleus is reprogrammed from a state of unipotency, which is proper to a somatic cell, to the totipotent state that is proper to the zygote. Now, in ANT-OAR the modification of the nucleus before the transfer consists in the forced expression of some of the factors that are associated with pluripotency. The goal of this is to force the process of reprogramming to result in the state of pluripotency, presumably without the new entity's ever entering the state of totipotency. This procedure seems to avoid some of the problems associated with ANT-1, namely, that the product of ANT-1 shares some of the developmental stages of the embryo. This problem appeared to be overcome, thus allowing some early critics of ANT-1 to be able, now, to endorse ANT-OAR. As a result, the original proposal aside has been largely set aside and discussion has centered instead on ANT-OAR.

I think, however, that it is worth continuing the discussion around ANT-1 within the context of Systems Biology in order to clarify both the arguments presented by its supporters and the problems raised by its critics. In a second section I will show how this analysis proves useful for making a better judgment of ANT-OAR.

1. The first proposal of ANT and Systems Biology

The rationale for supporting ANT-1 is based on a particular understanding of Systems Biology. I will follow here an article by Father Nicanor Austriaco, O.P., in which he explains this approach and how it can be useful for discerning the origins of human life.[2] After a presentation of Austriaco's argument, I will proceed to expose some difficulties involved in this approach and I will try to point to a solution.

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[2]Cf. Nicanor Austriaco, O.P., "On Static Eggs and Dynamic Embryos: A Systems Perspective," *NCBQ* 2 (2002): 659–683. The article was quoted in Hurlbut's testimony before the President's Council on Bioethics, which took place on 3 December 2004. See also Nicanor Austriaco, "Immediate Hominization from the Systems Perpective," *NCBQ* 4 (2004): 719–738; and Maureen L. Condic and Samuel B. Condic, "Defining Organisms by Organization," *NCBQ* 5 (2005): 331–353.

1.1 Systems Biology and the criterion of the future development of an organism

How can we determine the ontological status of an embryo? An external observer might be tempted to describe the embryo as a clump of cells. Systems Biology offers an attempt to overcome this view and to present a richer account of reality by understanding the living being as a "dynamic network of integrated parts."[3] This means that Systems Biology takes into account both the *structure* and the *dynamics* of these parts, in order (a) to describe the whole in an integrated way (structure) and (b) to see how it develops in time (dynamics). It is important to note here that structure and dynamics are tightly linked together. The chain of reactions between the parts is understood in a deterministic way, such that, given the original situation, we can predict the future path of the organism.

> An organism . . . is a deterministic system that follows a particular developmental trajectory. In other words, there is a causal relationship between the past, present, and future states of a living system because the molecular composition of the organism constrains the possible sequence of ordered transformations through which the system can advance.[4]

According to this perspective, even if the observations about the way the organism works in its early stages of development are not clear enough to decide about its ontological status, we still have a crucial criterion at our disposal: the determinism of the developmental process enables us to make predictions about how the entity will develop.[5] In other words, one must consider the whole process of development of the entity in order to arrive at a judgment of it. Since there is "a causal relationship between past, present, and future," the future will reveal the present and past of the organism.

Austriaco uses this deterministic notion of causality, which implies a tight connection between past, present, and future, to show the impossibility of establishing a moment in the process of development (a moment of enough organization or maturity) after which we

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[3]Austriaco, "On Static Eggs," 661.

[4]Ibid., 662.

[5]Ibid., 667–668.

can speak of human life, but before which we cannot.[6] We have thus a continuum that ensures that the embryo is a human organism from the beginning of fertilization on.

Austriaco has characterized his approach in the following way: "Thus, the emphasis now moves from what the fertilized egg looks like to what it does."[7] I think the idea could be more precisely expressed by replacing "what it does" with "what it will do in the future," that is, how it will develop. This is the point of emphasis in his approach. The observation of the present moment, what it "looks like" now, becomes irrelevant.

It is important to note that, for Austriaco, this irrelevance does not mean that the present moment is unimportant, but only, rather, that it does not provide us with an observable criterion by which to differentiate an embryo from a pseudo-embryo. The entity's present situation, taken by itself, is not sufficient for making this distinction, because the entity's active potentialities are not yet visible, not yet at play. The real structure of the entity now depends on what we can ascertain, on the basis of causal determinism, about how it will develop dynamically in the future. The real structure now is revealed only retroactively in light of the future dynamics of the organism.

This criterion is applied to ANT-1 by Austriaco in the following way. Since the entity produced will not develop as a human entity does, then it follows that it never was a human entity. The development of the being in question shows us that there was no human structure at the beginning. The absence of this structure, though displayed only in later stages of development, provides us with the key for understanding what was really going on in the first stages and thus for understanding the essence of the entity in question.

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[6]That means that, in principle, we cannot be absolutely certain about the status of an organism until its death: "Paradoxically, this definition suggests that one cannot know with absolute certainty if a particular product of fertilization is an organism until it dies. Death later in development increases the likelihood that the cell-to-organism transition presumed to have taken place was real" (Austriaco, "On Static Eggs," 668). However: there are some ways in which we can know the future path of development of an organism while it is still alive. For example, the presence of some substances within the developing organism implies that it will never reach a certain stage of development. In this case we are able to make a judgment about this entity: it was never human (668).

[7]Austriaco, "On Static Eggs," 668.

1.2 An inconsistent approach

Now, the criterion of future development is able clearly to distinguish between an oocyte and an embryo because we can predict that both will develop in very different ways. The development of an embryo, for example, will last for years and will lead to very complex structures. An egg, on the contrary, will live only for a short length of time. Their respective *dynamics* reveal that their *structures* are entirely different: thus a clear ontological distinction can be made between these two entities.

Despite this initial plausibility, however, we have to say that the use of development as a criterion is not unproblematic, which we will illustrate by way of an example provided by Austriaco himself.

Anencephaly is an abnormal development that prevents the formation of the brain in a fetus. Austriaco poses the question: since the development does not arrive at the state of a full, autonomous human organism, are we to conclude that we never had an embryo or fetus? Austriaco says that this conclusion does not hold. What are his reasons? It is an invalid example, he explains, because the factors that cause this abnormal development are not intrinsic to the biological system; they consist primarily of a deficiency of folic acid in the mother during pregnancy.[8] Accordingly, this organism still has the active potentiality of becoming a child, that is, a potentiality that can be developed from within as an activity, as opposed to a passive potentiality that is only borne from without.

But then the question arises: what would happen if a gene were found whose modification before fertilization or cloning had the same effect of anencephaly? It would not suffice to say that the cause for this failure to develop is now external to the child. According to the presuppositions of System Biology, we would have

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[8]"Note that this discussion did not consider abnormal development caused by extrinsic factors. For instance, anencephaly, the condition where the developing infant does not have a brain, is a gross defect in human development which is thought to be linked to environmental factors, primarily a deficiency in folic acid in the mother during pregnancy. In cases like this, it is clear that the anencephalic infant at fertilization was a normal embryo whose later development went awry. Therefore, despite the obvious morphological abnormalities which must have arisen from abnormal system dynamics, the anencephalic child is still a human organism" (Austriaco, "On Static Eggs," 670, note 28).

to say that this entity had never been a human being. But this is counter-intuitive: the embryo generated in this way would be a defective human embryo and not a non-human entity.

An attempt has been made to overcome this problem by introducing a further distinction: the difference between a lack of development of a part of the organism and a lack of development of its global structure.[9] The criterion of future development would be applied in a different way following this distinction. In a case, for example, in which only a part of the organism (for example, the heart) failed to develop, this criterion would tell us that we were in the presence of a human being, albeit a defective one. Only in the second case, in which the corruption affects the whole of the organism, could it be said that the entity was never a human organism, not even a defective one. ANT-1 corresponds to this second case, because it results in a total lack of structure and organization in its product.

It seems to me that this distinction does not help to solve the problem. What would happen if the modification of a gene causes the absence *of the structure of the whole* only at a later stage of development? According to the criterion of the future development, we would have to conclude, looking backwards, that the entity was not human from the beginning: a human organism does not develop into a tumor.[10]

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[9]Cf. Condic and Condic, "Defining Organisms by Organization," 331–353: "Defective human organisms are distinguished from non-organismal entities by agenesis of parts or malformation of parts, *but against a background of globally coordinated development*" (339). "To adequately define an entity as non-organismal, the sole criterion would be the failure to *organize* along an overall, coordinated pattern of human development" (340).

[10]This problem was already raised in the White Paper from the President's Council on Bioethics: "But suppose a useful genetic modification were achieved that entailed chaotic and disorganized development only at a *later* stage of embryonic (or even fetal) development. Could not the *ethical reasoning* in defense of ANT be used to argue that such further developed but still inherently defective entities are "fetuslike but not actual fetuses," and hence ethically suitable for exploitation and destruction? [...] It would certainly be troubling if the ethical case for ANT could be used to justify the creation and destruction of fetus-like entities. Hurlbut's proposal, seeking a source of pluripotent human stem cells, confines its attention to the early stages of embryonic development. But someone looking for a source of tissues or even primordial organs might be tempted to apply his reasoning to later and later stages of development, not excluding the deliberate

The problem can be formulated more generally. Suppose we are able to change, prior to nuclear transfer, a gene of the somatic cell nucleus that will prevent the further development of the whole entity after a certain amount of time. It is clear that, if this amount of time is one year, the organism will reach birth as a normal baby, the defect being manifested only later on, and we would have no doubt about its status as a human being. But what if this time is shortened to nine, five, three months or even a week or some hours? The organism would have an active potentiality to develop only up to this certain amount of time. Would we be able to determine the precise moment that makes the difference between human and non-human? Could we say, for example, that if the organism had the "active potentiality" to develop only up to the first month, then it was human, but not if it were able to develop only up to the first week?

Maureen and Samuel Condic have attempted to address this question by studying the first stages of embryo development. They have distinguished three crucial moments in the formation of the entity's structure and have discussed what degree of organization is sufficient for a human organism.[11] Other scholars have posed the question in the same way, trying to find the exact point in the development at which a minimal structure is achieved.[12]

I find this approach problematic. It poses, again, the question of a specified moment in which we could say that the organism has

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production of anencephalic fetuses or even newborns, useful as a source of organs and tissues. Hurlbut's criterion for being a truly human organism— "organization of the species-typical kind"—would appear to be inherently malleable and open to interpretation (and even mischief)" (*White Paper: Alternative Sources of Pluripotent Stem Cells*, text available at www.bioethics.gov/reports/white_paper/index.html).

[11]Cf. Condic and Condic, "Defining Organisms by Organization," (343). The stages are: 1. Separation of the earliest cells into two classes; 2. Gastrulation of the embryo proper; and 3. Integrated generation of the major organ systems.

[12]Cf. J. Huarte and A. Suarez, "On the Status of Parthenotes. Defining the Developmental Potentiality of a Human Embryo," *NCBQ* 4 (2004): 755–770: "We have witnessed in recent years a proliferation of procedures that make use of human germinal cells and human stem cells for therapeutic ends. These procedures generate organisms having very different developmental potentialities. To decide the legitimacy of these procedures, we believe that it is crucial to define the minimal developmental potentiality that an organism must have in order to be regarded as a person . . . " (769–770). Here there is also an attempt to distinguish several stages; see pages 759–760.

arrived at the minimum for being considered human. By so doing, it goes against one of the achievements of Systems Biology, which has demonstrated that there is not such a moment: the whole process is a continuum and, from the very beginning of the development, from the beginning of fertilization on, the embryo is a human individual. According to Austriaco, "the systems perspective . . . sees the distinction between sperm penetration, union of pronuclei (syngamy), and any of the later events in embryogenesis . . . as conventional and . . . arbitrary designations of points within a single continuum of developmental change."[13]

With this, we are able to recognize that it is insufficient to adopt the criterion of future development alone in order to determine whether we are in the presence of human life. Our examination has shown that the criterion of future development, if left to itself, is reduced *ad absurdum*. The purpose of this criterion was to demonstrate the continuum of life from its beginning, so that no exact point could be determined at which the embryo "became" human. But now proponents of Systems Biology have ended up searching once more for precisely this discrete point after fertilization at which a sufficient organization would allow us to speak of an embryo and not a pseudo-embryo. Of course, I do not deny that an organization is needed in order to speak of an organism. What I deny is the validity of the attempt to specify the minimal organization required in order to speak of a human being. An organization is present from fertilization on, and the growth in organization is a continuum in which there are no clear boundaries. The organism has

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[13]Austriaco, "On Static Eggs," 673. Cf. the critique by Richard Egan in his Colloquy submission,"The Burden of Proof," *NCBQ* 5 (2005): 12: "After his presentation to the President's Council on Bioethics, Dr. Hurlbut was asked by Professor Meilaender how his proposal would differ from a hypothetical proposal to produce an entity which 'had the capacity to implant but would absolutely not develop beyond eight weeks.' In his reply Dr. Hurlbut at first suggested that any entity unable 'to form the infrastructure and body plan of a human organism' would not be a human organism. Then he appeared to pull back: 'I think that's too far. I would go back to the most primary lineage differentiation,' that is, the differentiation between the trophectoderm and the inner cell mass. It is hard to see why the deliberate disabling of this entity so that it falters at a very early stage of normal human development makes it necessarily ontologically different from an entity deliberately disabled so that it will falter at any later stage in its development prior to reaching the mature human form. Simply pointing out that this is the 'most primary lineage differentiation' fails to establish this ontological difference."

to be conceived of as an interlocking whole that comes into being all at once, and then develops itself from then on, remaining constant throughout a series of changes of structure, all of which express it.

1.3 An additional criterion

We have shown that Austriaco's criterion of future development is insufficient in order to determine the presence of human life. In our search for a complementary criterion, let us turn to the different understanding of the organism behind Roberto Colombo's critique of ANT-1. As Colombo writes in a recent article:

> The concept of organism underlying the argument in favor of ANT [Colombo refers here to ANT-1] is questionable. From a biological (systematic and integrative biology) and philosophical (philosophy of biology) point of view, a living organism—i.e., a living being—is characterized by its intrinsic morpho-functional unity (integration and coordination of the biological parts, such as cells, tissues, organs, etc.), not by its capacity to progress to an advanced stage of development or to a more mature status. A human embryo is a human organism not because it will become a fetus or a newborn baby, but as a result of the intrinsic unity (*indivisum in se*) of its cells, which act as a whole and not as the sum of its parts.[14]

Colombo stresses that an organism is discerned through examination of its present way of being, that is, by its intrinsic morpho-functional unity, and not by its future development. The difference can be expressed thus: in his analysis, Austriaco focuses only on the future of the organism, while Colombo takes into account the dynamics of the present stage of development, as well.

Note that here two different consequences of the principle *agere sequitur esse* are implied: one that looks to the future, the other to the present. *Agere sequitur esse* can mean that the way an entity will have acted in the future reveals its being in the present. Austriaco uses the term in this sense. If it ends up looking like an adult human being, then it was already a human organism even in the earliest

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[14]Cf. Roberto Colombo, "Altered Nuclear Transfer as an Alternative Way to Human Embryonic Stem Cells: Biological and Moral Notes," *Communio* 31, no. 4 (Winter 2004): 645–648.

forms of development. But *agere sequitur esse* can also mean that the way the entity acts now follows the way it is now. If it now looks like an embryo or a fetus and acts like an embryo or a fetus, then it is now a human organism, even if it will never become an adult because of one or more defects that will be manifested later but are not changing the present organization and dynamics of the organism. We could say that it is a defective fetus or embryo because of this inherent defect that will prevent its development.[15]

What I propose here is the adoption of a second criterion in order to determine the status of an entity. This does not mean that we have to dismiss the criterion of the future development. Rightly understood, this criterion of the future enables us to demonstrate, on the basis of the future appearance of a mature human being, the fact of its presence already at the embryonic stage. But this criterion cannot be used the other way around. The fact that the development is not achieved does not entitle us to affirm that there was no human form before. Thus, it is true that, if X will have developed as a human entity by time *b*, then it was also one at time *a*. The inference Austriaco draws from this is false, however: that is, it is not always and in every case true that, if the entity will fail at some future time to have developed like a human organism, then it is not an organism now. Otherwise, we could never distinguish between defective organisms and non-organisms.

The problem with Austriaco's point of view is that it is based on a deterministic account of the organism's development that equates its past with its future and excludes any possible novelty between them. But this account, which could be valid for a machine, is not valid for an organism, because the latter has a principle of inwardness whose action is not reducible to efficient and material causes. The development cannot be accounted for simply from the point of view of the interaction of particles. It is not enough, then, to consider the future path of growth of the

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[15]Austriaco applies the principle *agere sequitur esse* to defend the position that ANT-1 never shares any stage of a human development. His claim is that he concentrates on action as a sign of being in order to argue that, since the new entity is structurally incapable of performing certain typically human actions, it cannot be human. My point is that he applies this principle to refer to the future, and not to the present of the organism. The problem with his argument is that he is concentrating not merely on action as a sign of being, but on the capacity for *future* action as a sign of *present* being.

organism and then to judge retroactively about the previous stages of its existence.

This second criterion which I propose to adopt focuses on what Colombo calls "intrinsic morpho-functional unity (integration and coordination of the biological parts, such as cells, tissues, organs, etc.)" at every stage of development.[16] This criterion states that, if the intrinsic morpho-functional unity of a given entity during any stage of its development is coincident with the intrinsic morpho-functional unity of a human organism in any stage of its development, then this entity is human during this period of time. Note that this is not to say that every clump of human cells has to be ascribed the dignity of a human being. We have proposed here a clear principle for distinguishing between different organisms. Only if the entity under examination shares the trajectory of a human form for a period of time, is it necessary to consider it human during that time.

But how is this criterion to be applied? Austriaco could claim that it is very difficult to know whether something is a human organism by looking only at its present structure. This is true, because crucial differences are not easy to detect in these first stages.

And yet this does not mean that the criterion of the present morpho-functional unity cannot be applied at all. The task becomes easier in cases that can be compared with other organisms that we already know with certainty are human. We can take the entity in question and ask whether, future acquisition of a mature form aside, this entity shares any stages of development with an entity that we know is human.[17]

We could formulate this principle in the following way: if entity A shares one part of the trajectory with entity B, and entity B ends as a human being, then entity A has to be accorded the same dignity as entity B while it shares the same trajectory. In order to say

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[16]A philosophical consideration of the living organism would reveal the different understandings of the living being that undergird Austriaco's and Colombo's points of view. In order not to interrupt the flow of our argument, we will leave this analysis for the last section of this essay.

[17]The correct way to judge the status of an entity is to make comparisons with organisms whose status is already known. The comparison with teratomas and other organisms whose status (at least in the early stages of development) is not very clear seems to be an attempt of interpreting *obscura per obscuriora.*

that their ontological status is not the same we would have to locate different organic functions or a different organization that indicates a fundamental change in structure or dynamics *during the shared part of the trajectory*. If so, we could conclude that these two entities do not share the same trajectory after all. But if our criterion for establishing a difference refers only to the future, to some defect latent and not yet active in entity A, something that will only later begin to be functional, this fact does not allow us to treat entity A differently from entity B while both are operating in the same way.

In the concrete case of ANT-1, we have a clear point of comparison for our criterion: the product of regular SCNT. The case turns out to be even simpler because we can pinpoint the exact difference between the two: ANT-1 involves manipulation of the somatic cell nucleus before nuclear transfer, SCNT does not. In order to say that the product of ANT-1 is not a human organism, we would have to prove that the modifications introduced in the nucleus affect not only the future development, but also the present structure of *each moment* of the trajectory.

In fact, this same principle of the present structure was operative in some of the early critiques of ANT-1. Let us quote, for example, Edward J. Furton:

> In my opinion, there is every reason to believe that what would be produced under this proposal is a defective embryo. Hurlbut would deny this, but the fact remains that this entity will pass through several divisions of normal embryonic development before the engineered defect expresses itself and brings further progress to a halt.[18]

I would add: Hurlbut would deny this because he would use the criterion of future development as the sole criterion for determining the existence of human life. Furton is taking the criterion of the present morpho-functional unity into account as well: the entity shares some stages that are not distinguishable from a development of a human being after the initation of fertilization, and this other criterion allows him to accord this entity the dignity of a human life.

We see then why this objection is not answered by scientific research that observes future development alone. It is not anti-

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[18]Edward J. Furton, "A Defense of Oocyte-Assisted Reprogramming," *NCBQ* 5 (Autumn 2005): 465–468; 466.

science to say that an experiment about the development of the ANT-1 product will not alter a judgment about the present state of the entity. In this case, an experiment that can verify that the trophectoderm fails to form would not help, because both entities would still share the first stages of the development. The problem is that this particular kind of experiment does not answer the question: another kind of scientific research is necessary. The question to be answered is: is there any difference between the first stages of ANT–1 and the normal development of an embryo? Even before we conduct any experiments the answer seems to be negative, since the modifications introduced in the nucleus before the transfer were not intended to modify this first stage of development. Let us be clear: we are looking for a difference that is not based only on the future development of the entity, but rather on the present structure and dynamics of the organism.

2. Does ANT-OAR avoid this problem?

Of course, what we have just said applies only to ANT-1. ANT-OAR seems to avoid precisely this difficulty of sharing some stages of the development of a human life. This is why it has gained support from some scholars who were critics of the first ANT proposal.

What we encounter in ANT-OAR is a nuclear transfer with the activation of a selection of genes before the transfer. This change is intended to affect the process of epigenetic reprogramming so that the entity will never exhibit totipotency, which is proper to the single-cell embryo in its very beginning. Proponents claim that the product of ANT-OAR will only ever exhibit a pluripotent stage, which is proper to a stem cell. If such is the case, the product of ANT-OAR does not share any of the stages of an embryo. Following the logic of the ANT-OAR proposal, we could thus state: 1) The future development would not be that of a human being, since totipotency would never be exhibited. 2) This entity would never share the stages that are present in the development of a human being after normal fertilization. This is why it seemed logical to the proponents to go forward with the experiments.

I think, however, that another question needs to be answered first. Even if we grant that there are no shared stages in the development of the product of ANT-OAR and a normal embryo, there is

another human organism that could share some stages of development with the product of ANT–OAR: namely, the entity produced by normal somatic cell nuclear transfer (SCNT). We could thus apply our second criterion to these two entities. Do they share any of the early stages of development, in such a way that there could be no essential distinction in their form and function?

2.1 When does life begin for a product of SCNT?

The question that must be posed now is: what is the ontological status of the product of SCNT? Here it will suffice to apply the criterion of the successful future development, according to Systems Biology as presented by Austriaco, who states:

> With the birth of Dolly, it is now clear that somatic cell nuclear transfer is able to effect the same cell-to-organism transformation in the egg associated with fertilization, but in the absence of sperm. In other words, the introduction of a nucleus taken from a starved somatic cell obtained from an adult animal is able to transform the egg and prompt it to begin embryogenesis. The egg cytoplasm reprograms the donor nucleus such that the living unit is now a system where the molecular network is able to progress through normal development. Thus, from the systems perspective, the product of SCNT is properly called an embryo.[19]

It is, then, an established principle that the product of SCNT is human. However, we need to be more precise in our question and answer. In fact, two moments can be distinguished in the process of SCNT: (a) the moment in which a nucleus is introduced into the enucleated oocyte; and (b) the moment in which reprogramming has already taken effect. My question is whether the product of SCNT is a living being from moment (a) or only from moment (b) on.

It seems to me that this period of time has been disregarded in the discussion about ANT-OAR. Edward J. Furton, for example, describes ANT-OAR in the following way: "as soon as the nucleus is fused to the ovum, a cell having pluripotent properties exists."[20] But in order to have a cell with pluripotent properties, the process

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[19]Austriaco, "On Static Eggs," 677.

[20]Furton, "A Defense of Oocyte-Assisted Reprogramming," 446.

of reprogramming has to take place, at least part of it. That means that we do not have a single moment but rather a process of development. The existence of this period is very important, even if the time elapsed is a very short one.

This consideration of reprogramming as a single, simple event or occurrence seems to be present as well in the following statement by Austriaco:

> The enucleated egg must also be able to *reprogram* the transferred human genome, transforming it from a genome where only those genes associated with the donor cell type, say a human liver cell, are turned on, to a genome where only those genes associated with a single-cell human embryo are turned on. It is this second event—the reprogramming of a human genome into the epigenetic state associated with embryos—that is the essential event that constitutes a new human organism. This is the event that gives the single cell—now properly called an embryo—the intrinsic capacity to follow a self-driven, robust developmental pathway that manifests its species-specific organization.[21]

In this last statement the process of reprogramming is seen again as a single event or occurrence. But what we are trying to determine with our question is a more precise answer. Reprogramming is not a single moment, but is itself a process. What is the exact point in this development, from the moment when the somatic cell nucleus enters the egg, through the end of reprogramming, at which we can speak of a human being?

It seems to me that there are serious objections to option (b) (i.e., the starting point of human status is the finalization of reprogramming). Reprogramming, once it starts in SCNT, is a necessary step in the single process that will conclude, theoretically, with the birth of a child. What is the sense of reprogramming if not to allow the formation of an embryo? The dynamics of the cell in these first moments of reprogramming tend already towards enabling the complete formation of a human being. The very activity of reprogramming expresses an already existing system that functions towards a unified goal. It seems artificial and arbitrary to state that we have a human organism only at the moment when totipotency is achieved, but not before. The product of SCNT does not begin to

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[21]Nicanor Pier Giorgio Austriaco, O.P., "Altered Nuclear Transfer. A Critique of a Critique," *Communio* 32, no. 1 (Spring 2005): 172–176; here, 174–175.

be an embryo only after reprogramming, but already before it, once the donor cell nucleus is introduced in (fused with) the enucleated oocyte. This is the starting event that triggers the entire process.[22]

The same argument that Austriaco applies to normal fertilization can be applied as well to our question:

> the systems perspective highlights the seamless unity of the developmental process which begins with fertilization and ends with the death of the organism. It sees the distinction between sperm penetration, union of pronuclei (syngamy), and any of the later events in embryogenesis (for example, the stabilization of the diploid nucleus of the embryo) as conventional and, as above, arbitrary, designations of points within a single continuum of developmental change. Recall that all these morphological markers are simply manifestations of an ongoing process of molecular change. Thus, fertilization from the systems view is properly that moment when the whole chain of molecular events is set in motion, when the organism comes to be.[23]

My conclusion is that with SCNT, too, we have "a single continuum of developmental change," and that it would be arbitrary to say that the process of reprogramming is independent of the rest of the process of development. We should conclude, even from the systems perspective defended by Austriaco, that the status of the product of cloning from its very beginning is that of a human life.

2.2 A comparison of the products of ANT and SCNT

Let us now apply the principles determined in our first section to the product of ANT-OAR.

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[22]This is reinforced by the fact that the "event" of the end of reprogramming does not seem to be a clearly determinable point in the development process. It is even suggested that this "event" is not always totally achieved in cloning, which is the cause for the defects observed in some cloned living beings. Incomplete epigenetic reprogramming could also explain why some live-born animals suffer from subtle defects that sometimes do not appear for years. In this case we have living beings that did not achieve a complete reprogramming: cf. Bruce Stillman and David Stewart, eds., *Epigenetics,* Cold Spring Harbor Symposia on Quantitative Biology, vol. 69 (Cold Spring Harbor, N.Y., 2005), 19–20.

[23]Austriaco, "On Static Eggs," 673.

The first criterion, future development, is clear in regard to this entity. The entity will never reach the state of a mature human being, will never develop into an embryonic state. In order to prove this, the proposed animal experimentation could be useful.

But our point in (1) was precisely that this criterion of the future is not enough when the development fails. We have to inquire, as well, whether the product of ANT-OAR shares any of the stages of development of an entity that is known to be human.

If the analysis in (2.1) is correct, then we have to say that the answer is affirmative. The entity that results from ANT-OAR shares at least the initial stages of reprogramming with the product of SCNT.[24]

To deny this conclusion, and, thus, that the product of ANT-OAR is a human organism, at least for a period of time, it would be necessary to prove at least one of the following two points: (a) the product of SCNT is not a human organism until the conclusion of the reprogramming process; (b) there exists a real difference between the product of SCNT and the product of ANT-OAR during the process of reprogramming.

It does not suffice, then, to say that the product of ANT-OAR will never reach totipotency (this statement is grounded on the first criterion of future development only). We must avail ourselves of the second criterion (which we proposed following Colombo), as well.

It is clear that none of these points can be shown by the proposed experimentation. As Edward Furton states: "We will learn [from experimentation] whether the entity that results from OAR is pluripotent or totipotent."[25] Thus, if the experiment proves successful, it will show that the product of ANT-OAR never reaches the epigenetic state of an embryo. The question of whether or not the entity is human from the beginning will be left unaddressed, indeed, it will be begged. Conversely, if this part of the process (the earliest stages of the process after nuclear transfer) is considered already a part of the development of a human being, as it arguably

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[24]Cf. Tadeusz Pacholczyk, "Ethical Considerations in Oocyte Assisted Reprogramming," *NCBQ* 5 (2005): 446–447: "In OAR, the introduced somatic nucleus would only be partially reprogrammed towards a more primitive state by oocyte factors" (446).

[25]Furton, "A Defense," 468.

is, then the product of ANT-OAR would be sharing, during a certain period of time, in the process of the formation of a human being. So, the experiment will only prove something about the future development of the organism, and will not settle the question of what the organism is in its first moments of existence.[26]

The proponents of OAR have claimed that the presence of Nanog changes the whole entity *ab initio*. Do they mean by this that the reprogramming process takes no time and that Nanog brings the cell immediately to a pluripotent state? Or only that the reprogramming destines the entity *ab initio* to remain in the pluripotent state when this state is achieved? These two statements are different. The first possibility seems difficult to maintain: reprogramming involves material changes that necessarily take time. Such a proposal of an instantaneous reprogramming would be entirely fanciful, and not at all based in biological and developmental reality. What about the second possibility, according to which Nanog only prevents (*ab initio*) the entity from proceeding beyond the pluripotent state when reached? If Nanog is associated with pluripotency, its presence does not affect the first stages of reprogramming, in which pluripotency is not yet achieved. Nanog changes only the future, not the present of the organism. Hyperexpression of Nanog is relevant only according to the criterion of future development, not that of present morpho-functional organization. ANT-OAR may be thus reduced to the first scenario of ANT-1: the same reasons that support or oppose the first procedure will support or oppose the second one.

We can then conclude: if the foregoing argument is sound, the same problems that arose with regard to ANT-1 apply equally to ANT–OAR. The difference is that, with ANT–OAR, our inquiry remains at the level of the single cell entity, during the moment of reprogramming of the nucleus, before it reaches the state of pluripotency. It is this period of time that is interesting for our purposes. In order for the OAR proposal to hold water, an essential difference must be demonstrated between the entities produced by SCNT and

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[26]We can apply here the same reasoning used by Tadeusz Pacholczyk, "The Substantive Issue Raised by Altered Nuclear Transfer," *NCBQ* 5 (2005): 17–19, regarding the hydatidiform mole: "the conceptual question remains whether even such an aberrantly growing entity like a CHM [complete hydatidiform mole] may not initially pass 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" (18).

ANT-OAR during the time of reprogramming before the entity reaches pluripotency. This difference cannot be based on the presence or absence of a factor that is associated only with a stage of development (for example, pluripotency) that comes after the reprogramming process begins—after the fusion of the donor cell nucleus and the enucleated egg—because the whole question hinges on whether or not the new entity is human from that point on, and not just from the time of the completion of the reprogramming process.

Until a difference related to these first stages of reprogramming has been demonstrated, it must be maintained (at least by those who have reservations about ANT-1) that the product of ANT-OAR, during these first moments of its development, has the same status as the product of SCNT: that is, it is a human being.

Conclusion

In this paper we have dealt with two points that can be discussed separately.

(a) Supporters of the first ANT procedure (ANT-1) have justified the procedure using the criterion of future development. Their reasoning is that since this entity develops into a tumor, and human organisms do not develop into tumors, the product of ANT-1 is not a human being. We have shown that this criterion is not sufficient to settle the question regarding ANT-1. Even if the entity ends up becoming a tumor, we have no proof that it was not a human organism during the first stages of development. Another criterion becomes necessary, a criterion that takes into account every moment of the development of the entity. Does this entity have the same morpho-functional unity as a human being at any of its stages of development? If there is a moment in the development of the organism when we can answer this question affirmatively, then we are facing a human organism at this moment of its development. Following this train of thought, many scholars have rejected the ANT-1 procedure. The dissimilarity between a normal embryo and the product of ANT-1 (the fact that the *Cdx2* gene is switched off) makes no difference in the morpho-functional unity of the entity during the first stages because the *Cdx2* gene is associated with a later stage of the development, when the formation of the trophectoderm takes place.

(b) The product of ANT-OAR shares a part of the path of development of a known human organism (the product of SCNT). This conclusion is based on two points that may, in turn, be discussed separately.

(b1) The product of SCNT is a human organism beginning with the introduction of the nucleus into the enucleated oocyte, that is, it is a human being during the whole process of reprogramming.

(b2) The product of ANT-OAR and the product of SCNT are indistinguishable in their morpho-functional unity during the first stages of reprogramming. The dissimilarity between the two entities (the expression of Nanog) makes no difference in the morpho-functional unity of the entity during these first stages because Nanog is associated with a later stage of reprogramming.

The criteria pointed out in this article can help us determine the ontological status, not only of the product of ANT–OAR, but also of other entities that share stages of development with human organisms. □

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