Articles

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On Static Eggs and Dynamic Embryos: A Systems Perspective

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In a recent paper, Cibelli et al. obtained embryonic stems cells from nonhuman primate eggs that had been artificially induced to undergo the early stages of mammalian development without any contribution from sperm, a process that has been called parthenogenesis.[1] In these cells, all the chromosomes and thus all the genes are inherited only from the mother. This same group, working at Advanced Cell Technology (ACT) in Massachusetts, had already initiated similar experiments with human eggs but the development of these artificially activated ova did not reach the blastocyst stage at which point stem cell progenitors form.[2] Significantly, these authors suggest that this approach of obtaining embryonic stem cells, because it elimi-

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[1]J.B. Cibelli et al., "Parthenogenetic Stem Cells in Nonhuman Primates," *Science* 295.5556 (February 1, 2002): 819.

[2]J.B. Cibelli et al., "Somatic Cell Nuclear Transfer in Human Pronuclear and Early Embryonic Development," *e-biomed: The Journal of Regenerative Medicine* 2 (November 26, 2001) at www.liebertpub.com/EBI/default1.asp; accessed on December 1, 2001.

nates the requirement to produce or disaggregate a normal, competent embryo, "may circumvent the ethical concerns voiced by some, positively impacting the debate in stem cell research."[3] An implicit premise here, of course, is that the artificially activated human egg, called a human parthenote (also, parthenogenote or parthenogenone), is unlike the human embryo and therefore does not have equal moral status. But is this distinction real?

This question is only one of the many controversies surrounding the ontological status of biological entities at the beginning of life. A perusal of any bioethics journal will reveal that there is much talk in the current literature concerning the ontological nature of the gamete (egg or sperm), the stem cell, or the embryo.[4] In one case, bioethicist Ernle W.D. Young has equated the presentient fetus and the unfertilized ovum because he contends that both are equally potential human beings.[5] In another, Harriet Rabb, legal counsel, for then National Institutes of Health (NIH) director, Harold Varmus, argued that insofar as human embryonic stem cells themselves are not embryos, federal laws banning embryonic research do not prohibit funding for research on them.[6] These comments are all judgments on the ontological nature of eggs, stem cells, embryos, and fetuses, but again, are they true?

To this growing list of biological entities, we can now add the parthenote and the cloned embryo (or what one prominent scientist has chosen to call the product of somatic cell nuclear transfer suggesting that it is not an embryo.[7]) This essay will explore and clarify the ontological differences between the embryo, the parthenote, and these other biological entities by developing a conceptual framework that applies the insights of systems biology to the entities and events at the beginning of life. A systems perspective will allow us to better understand the biological processes that we call fertilization, cloning and now, parthenogenesis, by providing the meta-

[3]Cibelli et al., "Parthenogenetic Stem Cells," 819.

[4]For a discussion of the controversy over semantics, see G. McGee and A. Caplan, "What's in the Dish? Ethical Issues in Stem Cell Research," *Hastings Center Report* 29.2 (1999): 36–38.

[5]Ernle W.D. Young, "Ethical Issues: A Secular Perspective," in *The Human Embryonic Stem Cell Debate: Science, Ethics, and Public Policy*, ed. Suzanne Holland, Karen Lebacqz, and Laurie Zoloth (Cambridge, MA: The MIT Press, 2001), 163–174. A similar comment has been made by another bioethicist, R. Alta Charo, who has argued that every somatic cell is equivalent to an embryo because both are potentially an adult organism. See her essay, "Every Cell Is Sacred: Logical Consequences of the Argument from Potential in the Age of Cloning," in *Cloning and the Future of Human Embryo Research*, ed. Paul Laurtizen (New York: Oxford University Press, 2001), 82–89.

[6]Quoted by Erik Parens in "On the Ethics and Politics of Embryonic Stem Cell Research," in *The Human Embryonic Stem Cell Debate*, ed. Holland et al., 49. Also see M. Wadman, "Embryonic stem-cell research exempt from ban, NIH is told," *Nature* 397.6716 (January 21, 1999): 185–186.

[7]James A. Thomson, "Human Embryonic Stem Cells," in *The Human Embryonic Stem Cell Debate*, ed. Holland et al., 15–26. Dr. Thomson was the lead investigator of the team which first isolated human embryonic stem cells in 1998.

physical account of the embryo that should undergird any ethical discussion regarding the beginning of life. This paper will argue that from the systems perspective, the human parthenote generated at ACT, like the human gamete and the human stem cell is still a cell and not a human organism and as such is different in kind from the human embryo. Thus, any experimental procedures involving ACT's human parthenote, including techniques which could lead to its destruction, should be morally permissible.

A Systems View of Life

A product of the postgenomic explosion in biological information, systems biology is an emerging field of research that seeks to understand the living whole as a dynamic network of integrated parts.[8] Its goal is to uncover the fundamental design principles of living systems by looking at what systems theorists call a system's structure and its dynamics. An analysis of a system's structure identifies all the parts of the system and describes their interactions. In biology, this would involve cataloging all the molecules that go into assembling a living organism and then determining which ones interact with each other. An analysis of a system's dynamics focuses on the behavior of these interacting molecules over time. In biology, this would involve questions regarding growth, development, and maintenance of the living organism. As will be discussed below, the structure and the dynamics of a living system are inseparably interdependent. A living system is always molecules in motion. Thus, the most important question for the systems biologist is how both the structure and the dynamics of a living system together give rise to the physical properties and visible behavior of the organism.

The two insights of systems biology that are of particular interest to us here as we develop a systems-based philosophical account of embryogenesis are its emphases on the holism of the living organism and the determinism of animal development. First, the emphasis on holism. Consider the human body. The most common view is to see the human being as a collection of organs working together under the sway of the central nervous system. Another approach is to see the body as an organized collection of different kinds of cells—nerve cells, heart cells, or skin cells, just to name a few of the approximately 260 cell types in the human body—all working together in the organic whole. However, the more radical perspective offered by systems biology is to see the human organism as a dynamic, complex, and seamlessly integrated network not of organs nor of cells but of *molecules,* including DNA, RNA, lipids, and proteins, connected by reaction pathways which generate shape, mass, energy, and information transfer over the course of a human lifetime. In contrast to the prevailing reductionist and mechanistic view, the organism is seen here as a single, unified whole, a complex and dynamic network of interacting mol-

[8]For concise overviews of systems biology, see both L. Hartwell et al., "From molecular to modular cell biology," *Nature* 402.6761 (December 2, 1999): C47–C52, and H. Kitano, "Systems Biology: A Brief Overview," *Science* 295.5560 (March 1, 2002): 1662–1664. A good introduction to the systems perspective written for the nonscientist can be found in Stuart Kauffman, *At Home in the Universe: The Search for Laws of Self-Organization and Complexity* (New York: Oxford University Press, 1995).

ecules that appear and then disappear in time. It is an embodied process that has both spatial and temporal manifestations.

To illustrate the holistic perspective, we turn to a symphonic orchestra. One way to view a classical orchestra would be to say that it is made up of four groups of musicians playing a type of instrument, woodwind, brass, percussion, or string. Another is to say that it is made up of approximately ninety musicians. The systems view would be to see it as a single dynamic network of interacting parts where the whole is greater than the sum of the parts. Since each musician has an instrument and a score, the orchestra at a minimum has three hundred parts all organized and seamlessly integrated into a single unity that produces music. In fact, from the systems perspective, an orchestra is not truly an orchestra until its parts begin to interact with one another, i.e., when it is performing a symphony. Therefore, to see the living organism as a dynamic system is to see it as a symphonic whole where DNA, RNA, lipid, and protein molecules, like musicians and their instruments, appear and then disappear on stage in the choreographed performance called life.

As noted above, systems biology, in addition to emphasizing the holism of the organism, also underscores the deterministic nature of animal development. In this, there is a crucial difference between an orchestra and an organism. One orchestra can play many symphonies because the musical score determines how and when the different parts will interact. In other words, the same structure can give rise to different dynamics—the same parts of one orchestra can interact in different ways to produce either Beethoven's Ninth Symphony or Mozart's Symphony No. 40. Thus, one cannot predict the future performance of an orchestra from simply studying its parts. It is an indeterminate system. An organism, on the other hand, 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. A puppy cannot grow into an ostrich.

To illustrate the deterministic nature of development, our orchestra analogy will not suffice. Instead, take a hypothetical living network, say the simple organism of ten molecules diagrammed at time t=0 in the accompanying figure. When these ten molecules are in close proximity, they interact. As indicated in the figure, some of these interactions result in transformative reactions that generate new molecules, and the living system becomes the network of eight molecules diagrammed in the middle of the figure at time $t=T_1$. This system is deterministic because the system can only change in this one way—the identity of the molecules in the initial state of the organism at time t=0 determines the kind of change possible. Molecule A and molecule B, because they are what they are, interact and produce molecule D. Notice, however, that molecule D is then able to interact in a subsequent reaction with molecule C to produce more of A and E driving the organism to change into the network of nine molecules diagrammed at time $t=T_2$.[9] Thus, as this example illus-

[9]Note that the reactions do not end here because molecules F and E can further interact to create molecule G, which can then continue to react.

trates, an organism changes and progresses through a sequence of ordered molecular changes precisely because each subsequent step in a reaction pathway is driven by the products of the previous step. Furthermore, it demonstrates that there is an intimate link between structure and dynamics in living systems. To change the composition of a living system, say by changing either the kinds of or the relative abundance of the molecules in the system, is necessarily to change the dynamics and behavior of that same system. A corollary to this is that the only way to change the

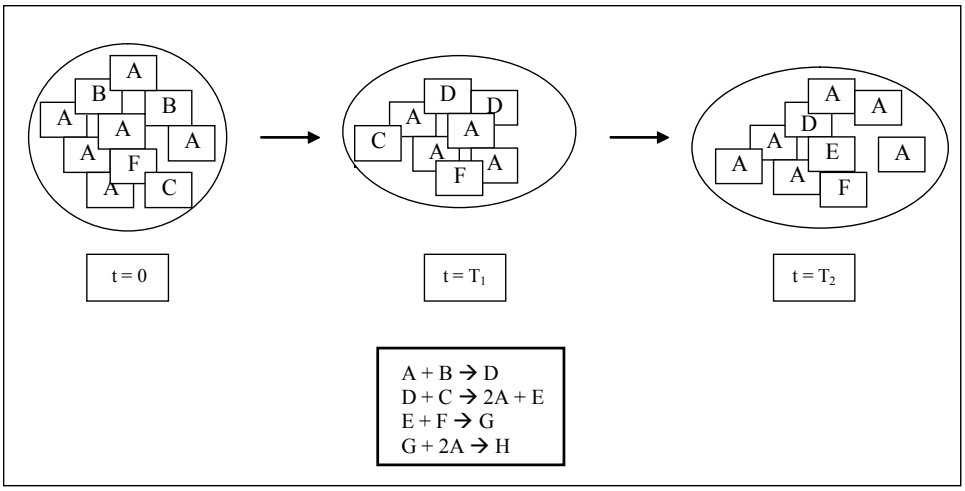

Figure 1: A Hypothetical Living Network

behavior of a living system is to change its molecular composition. Consequently, from the systems perspective, every developmental change, including the teething of an infant or the sexual maturation of a teenager, can be traced to transformations in the molecular composition of that particular human individual. In the end, animal development is like a falling chain of molecular dominoes that manifests itself as outward physical changes in the organism. Once the process begins, it is a self-driven, self-perpetuating chain reaction of molecular transformations that continues throughout the lifespan of the animal.

To summarize, the challenge of the systems perspective is to move beyond the hierarchical and static model of the living organism. Rather, the living system is seen as a unified whole, an embodied process of interacting molecules which has both a past and a determined future. This paper will argue that a philosophical account of the events and entities surrounding fertilization and embryogenesis that appreciates this holistic perspective can go far in clarifying many of the controversies in contemporary biomedical ethics.

A Systems View of Cells and Organisms

Before moving to a discussion of the beginning of life, however, there is one crucial distinction that needs to be made. This is the distinction between a cell and an organism. In most textbooks, the cell is often portrayed as a random soup of molecules enclosed in subcellular compartments defined by different membranes. Recall, however, that a cellular membrane is itself made up of molecules, specifi-

cally lipid molecules, which interact to form a sheet structure. Thus, from the systems perspective, the cell can be viewed as a three-dimensional constellation of interacting molecules that gives it its structure and its function. This focus on the molecular composition of the cell clarifies the differences among the approximately 260 cell types in the human body. Each cell type, from the systems view, is a unique subset of molecules encoded by a subset of the just over thirty thousand genes that make up the human genome.[10] The different shapes, behaviors, and functions of each cell type can then be readily explained by pointing to the necessary molecular interactions of each cell's unique panoply of molecules. Metaphorically, the molecules are engaged in a dance, a series of rhythmic and patterned interactions that gives the cell its identity and directs its life. Again, the cell is an embodied process.

If the cell and the organism are embodied processes, how then are they different? In essence, the former is dependent upon the latter. The human cell, as a living system, cannot survive on its own and requires the human organism for its existence. Even when severed from the organism and isolated in a tissue culture dish, the human cell relies upon a human organism, either the scientist or the lab technician, to maintain the appropriate laboratory conditions it needs to live. In contrast, the human organism is self-sustaining and able to survive as an independent entity throughout its lifespan. One biologist has defined the organism as "a discrete unit of living matter which follows a self-driven, robust developmental pathway."[11] To return to our analogy of the human organism as an orchestra, the human cell can be compared either to a section of the orchestra, say the violin section, or even to an individual musician, say the first violinist. The first violinist can attempt to perform a symphony on his own but he is usually associated with and dependent upon the orchestra for this task. Notice that the independence of a self-sustaining organism does not mean that it is autonomous or self-sufficient. Most organisms at sometime during their lifecycle depend upon others of their kind for their own survival. The unhatched chick relies on the hen, the jackal pup depends upon its parents, and *a fortiori*, the human being, fetus, infant, or toddler, depends upon other human individuals for his or her survival.

Finally, because of the diversity of life cycles present in nature, the distinction between a cell and an organism is sometimes blurred. For instance, the yeast cell is also the yeast organism. Here, however, we will focus on mammalian development

[10]Gene expression profiles have been published for twelve different tissue types. This human transcriptome map catalogs the activity of each of the nearly twenty-five thousand genes in each of these tissue types. They show that these tissues are fundamentally different at the molecular level. For details, see H. Caron et al., "The Human Transcriptome Map: Clustering of Highly Expressed Genes in Chromosomal Domains," *Science* 291.5507 (February 16, 2001): 1289–1292.

[11]B. Goodwin, "Development as a robust natural process," in *Thinking about Biology: An Invitation to Current Theoretical Biology*, eds. W. Stein and F.J. Varela (Reading, MA: Addison-Wesley Publishing Co., 1993), 123–148. Also see the essay by Juan de Dios Vial Correa and Monica Dabiké, "The Embryo as an Organism," in *The Identity and Status of the Human Embryo*, eds. Juan de Dios Vial Correa and Elio Sgreccia (Vatican City: Libreria Editrice Vaticana, 1998), 317–331.

and on human development in particular where there is a clear distinction between the organism and the cell as the whole is distinct from the part.

A Systems View of the Beginning of Life

At this point, we are ready to tackle the problem of fertilization and embryogenesis. First, a review of the biology with a description of the molecular and cellular events at the beginning of life.[12] Fertilization has traditionally been the point that marks the origin of the human organism. The process is initiated by fusion of the sperm and the egg, an event which usually occurs in the upper portion of the woman's fallopian tube. Between eleven and eighteen hours after insemination, the two pronuclei, one from each of the gametes, become visible and eventually unite forming the embryonic nucleus with its complete set of forty-six chromosomes. About thirty hours after sperm-egg fusion, the first cell division occurs, and two- to four-cell stage embryos can usually be observed by day two. By day three, the embryo reaches the eight-cell stage. Sometime between days two and three, the embryonic genome is activated representing the transition of control from maternally-derived to embryonically-derived molecules.[13] By day five, the embryo appears as a ball of cells, called the blastocyst, which is ready for implantation in his mother's womb. This sequence of orchestrated changes makes up the early stages of human development called embryogenesis.

Our analysis of the beginning of life from the systems perspective begins with the human egg or oocyte.[14] The egg is a cell. In fact, it is the largest cell in the human body. Most of the egg is composed of the cytoplasm that is chock-full of numerous RNA and protein molecules. If the egg were to encounter viable sperm, these molecules would support the process of fertilization and the first two cell divisions of a future embryo. Until fertilization, however, the mature human oocyte is a living system in stasis, a state called meiotic arrest. In a sense, the egg is a structured collection of inert molecules awaiting activation. Work over the last two decade has shown that a key regulator that maintains the meiotic arrest of the egg is a molecule called cyclin B.[15] In this frozen state, the egg only has a lifespan of about

[12]For details and citations to the scientific literature, see the review by F. Devreker and Y. Englert, "In vitro development and metabolism of the human embryo up to the blastocyst stage," *European Journal of Obstetrics, Gynecology and Reproductive Biology* 92 (2000): 51–56.

[13]To avoid any possible confusion, we should note that maternally derived molecules refer to molecules that were present in the original egg. They are not molecules that are introduced into the embryo after fertilization. Embryonically derived molecules, on the other hand, are molecules that are synthesized *de novo* after fertilization has already occurred.

[14]Why the egg and not the sperm? As will be discussed below, the egg can be transformed into an organism in the absence of sperm because in itself, it contains the molecular components necessary for establishing the body plan of the organism. Isolated sperm do not have this capacity. Thus, the egg is the more important of the two gametes.

[15]For a review of the molecular events associated with meiotic arrest and activation, see A. Abrieu, M. Doree, and D. Fisher, "The interplay between cyclin-B-Cdc2 kinase (MPF) and MAP kinase during maturation of oocytes," *Journal of Cell Science* 114.2 (January 15, 2001): 257–267.

twenty-four hours once it is expelled by the ovary. It cannot maintain itself and soon depletes its energy resources. If it is not fertilized, the system will deteriorate, collapse, and the egg will die.

From the systems view, the fusion of egg and sperm has two effects. First, it introduces new paternally derived molecules into the network of maternally derived molecules, which is the egg. Thus, the composition of the system is radically altered. Indeed, since it has a new structure, it is in fact a new system. As explained above, however, the composition and the behavior of a deterministic system are necessarily linked. Thus, fertilization also triggers a change in the dynamics of the egg by reorganizing and activating the interconnected network of inert maternal molecules in its contents. For instance, some one to three *minutes* after sperm and egg unite, there is an explosive increase in the levels of calcium within the cell which triggers the destruction of cyclin B.[16] As noted above, cyclin B is the key molecular inhibitor of cellular activity in the egg. Loss of cyclin B then triggers the chain of reactions and molecular interactions that drive cell division and differentiation. If left alone, this self-driven, self-perpetuating process of molecular interactions will continue for nine months and beyond, transforming the living system called an embryo into the living system called a gurgling eight-pound baby. Whereas the living system before fertilization only had a lifespan of twenty-four hours, the new living system after fertilization now has a span of seventy years or eighty for those who are strong. Furthermore, since this new system is capable of independent and self-sustaining existence, it is an organism. Fertilization is the paradigmatic example of the cell-to-organism transition.

Returning once again to our orchestra analogy, human development can be compared to the process of constructing and assembling an orchestra. At fertilization, the conductor-to-be is given the go-ahead to begin constructing and assembling every part of his future orchestra. However, this process has to be accomplished in a sequential manner. Our conductor-to-be may have to begin by crafting a violin and hiring a violinist. Together they then construct and assemble the remainder of the violin section. Next, the violin section constructs and assembles the percussion sections, and the orchestra grows as one instrumentalist after another is added to the group. Once started, the process, in theory, is self-driven and continues until the orchestra of ninety-six musicians is assembled. In fact, to be accurate, since animal development properly ends with death, this example would have to point out that the process is not complete when the orchestra is assembled but continues through the lifespan of the orchestra. The "development" of the orchestra would only end when the orchestra is disbanded.

In sum, from the systems perspective, the beginning of life should be understood, first and foremost, as the transformation of one dynamic system, the egg, into another, the embryo. The egg is a cell, an embodied process in stasis that only has a life expectancy on the order of hours because it is not self-sustaining. It is unable to

[16]For a review of all calcium-regulated events in early embryogenesis, see J. Carroll, "The initiation and regulation of Ca^{2+} signalling at fertilization in mammals," *Seminars in Cell and Developmental Biology* 12.1 (February 2001): 37–43.

meet the energy demands needed for survival. In contrast, the embryo is an organism, an embodied process that has a life expectancy on the order of decades precisely because it has the capability to sustain itself as an independent entity. It is a dynamic system which arises from the necessary interactions among the mix of molecules that is created by the fusion of the egg and the sperm, and it manifests itself as the visible and morphological changes which we call human development.

Abnormal Development and Embryogenesis

From the systems perspective, fertilization is the most critical event in the life of an organism because it effects the cell-to-organism transition that initiates a species-specific developmental trajectory. This, of course, is just a re-formulation of the traditional conception of the beginning of life. However, this does not mean that the embryo should simply be defined as a fertilized egg as many individuals believe. Rather, the human embryo is an embryo because it is a dynamic system that is in the initial stage of undergoing those changes associated with human development, a deterministic process that can span a century. This distinction between the embryo and the fertilized egg is important because fertilization is not one-hundred-percent efficient. At times, it can result in an embryo-like collection of cells which is incapable of undergoing normal human development. The often-cited example of this is the hydatidiform mole.[17] In a partial mole, two sperm fertilize an egg resulting in a conceptus with sixty-nine chromosomes. In a complete mole, the product of conception has forty-six chromosomes but all of them are derived from the father. (In contrast, recall that a normal human embryo has forty-six chromosomes, twenty-three from his mother and another twenty-three from his father.) Regardless of origin, however, hydatidiform moles always develop into a disorganized mass of placental-like structures that can become a malignant tumor. From the systems perspective, the abnormal morphology of the mole must arise from abnormal system dynamics implying that the mole, from the very start, did not have the requisite molecular components and interactions that define the embryo. Thus, the mole is more properly called a pseudo-embryo since it has neither the same system structure nor the system dynamics characteristic of the embryo and normal embryogenesis. Several bioethicists have reached the same conclusion by arguing that the mole is not an embryo, since embryos by definition do not become tumors.[18] Again, the common insight here is that an embryo is more than just a fertilized egg.

Thus, the question of the ontological status of entities at the beginning of life is really the question of distinguishing embryos from pseudo-embryos, a task that is not as straightforward as it may seem. First, as we have already noted, the fertilization of an egg is an insufficient criterion for identifying an embryo. Furthermore, abnormal examples of embryogenesis and human development, like the hydatidiform mole,

[17]For a review, see I.-M. Shih and R.J. Kurman, "Molecular Basis of Gestational Trophoblastic Diseases," *Current Molecular Medicine* 2.1 (2002): 1–12.

[18]See the discussion in Benedict Ashley, O.P., and Albert S. Moraczewski, O.P., "Is the Biological Subject of Human Rights Present from Conception?" in *The Fetal Tissue Issue*, eds. P.J. Cataldo and A.S. Moraczewski, O.P. (Braintree, MA: The Pope John XXIII Center, 1994), 37–38.

demonstrate that any morphological criteria can only be used with some difficulty to distinguish these two types of entities. Many perfectly "normal looking" embryos inexplicably stop dividing, while some embryos with gross abnormalities including darkened regions or voids go on to produce perfectly normal children.[19] Hence, visible characteristics especially early in embryogenesis can be misleading. Instead, the systems perspective proposes that an embryo should be defined as an egg whose molecular components as an ensemble have undergone a change such that their collective behavior over time is the developmental process we call embryogenesis. Thus, the emphasis now moves from what the fertilized egg looks like to what it does. 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. Fortunately, recent advances in developmental biology have provided a scientific framework that can be used to better distinguish embryos from pseudo-embryos while they are still alive.

For the purposes of our analysis, the most important insight of genetic research into the regulation of embryogenesis is that there are two kinds of genetic mutations which can affect human development. First, there are mutations in certain genes which render embryogenesis impossible. For instance, the Oct-4 transcription factor encoded by the *Oct-4* gene is one critical gatekeeper for mammalian development directing the growth of the embryonic stem cells that give rise to the different tissues of the embryo.[20] Loss of Oct-4 leads to nonimplantation and early embryonic death due to a failure to form the stem cell progenitors in the blastocyst.[21] This study defines a class of mutations, mutations which have effects early in development, which cannot be tolerated in embryogenesis, leading to system collapse. From the systems perspective, these system-disruptive mutations must be mutations in essential molecules that play a key role in the network of interactions which characterize a living system. Losing these molecules would be equivalent to generating gaps in a row of toppling dominoes. Both abruptly disrupt the chain reaction. The existence of this class of mutations may explain why in man, a high percentage of preimplantation embryos experience developmental arrest before the blastocyst stage.[22] For the most part, the reasons for this remain unknown

[19]R.T. Scott, Jr. et al., "Embryo Quality and Pregnancy Rates in Patients Attempting Pregnancy Through In Vitro Fertilization," *Fertility and Sterility* 55.2 (1991): 426–428.

[20]For a review, see M. Pesce and H.R. Scholer, "*Oct-4*: Gatekeeper in the Beginnings of Mammalian Development," *Stem Cells* 19.4 (July 2001): 271–278.

[21]J. Nichols et al., "Formation of pluripotent stem cells in the mammalian embryo depends on the POU transcription factor Oct-4," *Cell* 95.3 (October 30, 1998): 379–391.

[22]K. Hardy, A.H. Handyside, and R.M.L. Winston, "The human blastocyst: cell number, death and allocation during late preimplantation development *in vitro*," *Development* 107.3 (1989): 597–604. Note that this study was done using IVF embryos under artificial conditions in the laboratory. Studies involving IVF embryos may not necessarily reflect the general population, since most people who seek IVF are having infertility problems. A more recent study of pregnancy in 189 women reported that twenty-five percent ended in early loss before the sixth week after the last menstrual period of the woman, a number signifi-

and it has been attributed to a wide variety of causes including gross chromosomal abnormalities, failure to activate the embryonic genome, cytoplasmic fragmentation, and damage which reduces the developmental competence of the egg. In all these abnormal cases, however, what is clear is that the products of fertilization were mutated. They did not have the requisite molecular components that are needed for them to progress to maturity. Abnormal dynamics comes from abnormal structure. Therefore, the systems perspective suggests that those products of conception which bear mutations that distort normal embryogenesis, like the hydatidiform mole, are properly not and should not be called embryos. They too are pseudo-embryos.

In contrast, there are genetic mutations which can sometimes be tolerated by embryogenesis and human development. These would be system-nondisruptive mutations. In our own species, though ninety-nine percent of human embryos that lack a sex chromosome (Turner's Syndrome) are spontaneously aborted, a few are born with severe congenital defects and mature to adulthood, some even going on to bear healthy normal children.[23] This is only one example of how animal development can tolerate much error and variation without collapsing. In the lingo of systems theory, the living system manifests the property of robustness.[24] Though errors early in embryogenesis are often fatal, it appears that the maturing organism is able to tolerate more flaws as development progresses and still survive. One reason for this is that redundant genetic, molecular, and cellular pathways may come into play, averting system collapse. This may explain why a recent study has shown that though all cloned animals have genetic and epigenetic problems, some have survived to maturity.[25] Much research in systems biology is now attempting to understand the basis for the inherent stability of living systems such that they are able to

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cantly lower than other figures cited in the past literature (forty-five percent and higher). See A.J. Wilcox, D.D. Baird, and C.R. Weinberg, "Time of Implantation of the Conceptus and Loss of Pregnancy," *New England Journal of Medicine* 340.23 (June 10, 1999): 1796–1799.

[23]Margaret Thompson, Roderick R. McInnes, and Huntington F. Willard, *Thompson & Thompson Genetics in Medicine*, 5th ed. (Philadelphia: W.B. Saunders Company, 1991), 217. Also see the review by O. Hovatta, "Pregnancies in women with Turner's syndrome," *Annals of Medicine* 31.2 (April 1999): 106–110.

[24]For discussion, see N. Barkai and S. Leibler, "Robustness in simple biochemical networks," *Nature* 387.6636 (June 26, 1997): 913–917. For a nontechnical commentary on this paper, see L. Hartwell, "Theoretical biology: A robust view of biochemical pathways," *Nature* 387.6636 (June 26, 1997): 855–857. To illustrate the property of robustness, we return to our musical analogy. Orchestras too exhibit robustness. A single orchestra can tolerate a wide range in the caliber of its musicians and of their instruments. For instance, the musicians of the New York Philharmonic Orchestra could exchange their instruments for the instruments used by the local high school orchestra and still play Beethoven's Ninth Symphony. The quality of the performance may (and would probably be) different, but it is still the Chorale Symphony.

[25]See both D. Humpherys et al., "Epigenetic instability in ES cells and cloned mice," *Science* 293.5527 (July 6, 2001): 95–97, and F. Xue et al., "Aberrant patterns of X chromosome inactivation in bovine clones," *Nature Genetics* 31.2 (June 2002): 216–220. For commentary, see I. Wilmut, "Are there any normal cloned mammals?" *Nature Medicine* 8.3 (March 2002): 215–216.

handle the mutations which fall into our second class of genetic abnormalities.[26] From the systems perspective, these system-nondisruptive mutations must be in molecules that only have a peripheral role in defining the interactions which drive the development of the living system. The overall developmental trajectory of the network basically remains intact.[27] Thus, products of fertilization which bear mutations of this type should properly be called embryos since they could conceivably develop to maturity. Children born with Turner's Syndrome are still children. In spite of the altered system dynamics associated with their congenital defects, they are still bona fide human organisms.

To summarize, the fertilization of an egg is insufficient criteria for calling the product of fertilization an embryo, because fertilization does not always effect the cell-to-organism transition. At times, it gives rise to pseudo-embryos, embryo-like entities which are unable to progress through the normal developmental trajectory characteristic of the species, presumably because of inherent genetic or epigenetic mutations. Recent work in developmental biology has identified two classes of mutations which affect embryogenesis. Mutations which absolutely disrupt human development prevent the cell-to-organism transition from taking place because they occur in molecules that have essential roles in specifying the interactions which define and drive the embryo. Thus, products of fertilization which bear these mutations are properly called pseudo-embryos. On the other hand, mutations which only modify development, even grossly, do not impede the cell-to-organism transition since they presumably occur in molecules which do not have defining roles in specify the network of interactions which characterize normal embryogenesis. Thus, products of fertilization which bear this second type of mutations are properly called embryos even though they may be congenitally deformed.[28]

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[26]For instance, see the two studies, A. Becskei and L. Serrano, "Engineering stability in gene networks by autoregulation," *Nature* 405.6786 (June 1, 2000): 590–593 and B. Houchmandzadeh, E. Wieschaus, and S. Leibler, "Establishment of developmental precision and proportions in the early *Drosophila* embryo," *Nature* 415.6873 (February 14, 2002): 798–802.

[27]This statement has to be nuanced. In the ninety-nine percent of Turner's Syndrome embryos who died, the lack of a sex chromosome disrupted development, suggesting that in these particular individuals, the missing chromosome had an essential role in embryogenesis. However, the survivors do demonstrate that human development, in theory, can tolerate the absence of this chromosome and still generate a recognizable human being. Thus the absence of the chromosome may not have to affect the basic developmental trajectory of the mutant embryo who could conceivably develop to maturity as a Turner's Syndrome baby. The benefit of the doubt must fall on the side of life given the dignity of the human person.

[28]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. For commentary, see B. Ashley, O.P., "Moral Principles Concerning

Resolving Controversies Using the Systems Perspective

The systems perspective of the beginning of life just described can bring some clarity to five controversies within the bioethical literature. First, it emphasizes that human development from the beginning involves the cooperation of molecules, and thus of cells. Recent research has shown that the specification of positional information in the mammalian embryo by the sperm entry point demonstrates that the earliest two-celled mammalian embryo is a two-celled individual and not two individual cells.[29] From the very beginning, there is cooperation among the cells of the embryo, and the embryo manifests an integrity characteristic of intact organisms. It is a single molecular network. This discovery undermines the argument of those who have argued that the early human embryo is not properly a human being because it does not possess individuality, the case of monozygotic twins not withstanding.[30] Developmental plasticity does not necessarily preclude individuality.

Second, the systems view emphasizes the dynamic nature of life. The human body is in a constant state of flux. Decades of kinetic and metabolic studies using a variety of experimental techniques suggest that ninety-eight percent of the atoms of the adult human body, including those found in the brain and nervous system, are replaced in about two years.[31] Contrary to the philosophical views of many contemporary ethicists, this finding supports a traditional substantial view of the living organism, because anyone who rejects the distinction between living substances and nonliving aggregates would have to conclude that he or she can only exist and be identified as a distinct and unique human individual for a maximum of two years.[32] This, I believe, is obviously ludicrous.

Third, the systems view highlights the fact that an organism is precisely a living system undergoing that process of change which we call development. By definition, an orchestra is not an orchestra until it is fully assembled. Therefore, half an orchestra is not an orchestra. This is not the case with a living organism. There is no point during development when the organism is not an organism. Development does

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Infants with Anencephaly: Observations on the Document," *L'Osservatore Romano*, September 23, 1998, 8.

[29]For details, see my essay, "The Pre-implantation Embryo Revisited: A Two-celled Individual or Two Individual Cells?" *Linacre Quarterly*, forthcoming. For a recent study on this topic which appeared while my essay was in press, see B. Plusa, K. Piotrowska, and M. Zernicka-Goetz, "Sperm entry position provides a surface marker for the first cleavage plane of the mouse zygote," *Genesis* 32.3 (March 2002): 193–198.

[30]For representative formulations of this proposal, see N. Ford, *When Did I Begin? Conception of the Human Individual in History, Philosophy, and Science* (Cambridge: Cambridge University Press, 1988), 116–131; and H. Kuhse and P. Singer, "Individuals, Humans, and Persons: The Issue of Moral Status," in *Embryo Experimentation*, eds. P. Singer et al. (Cambridge: Cambridge University Press, 1990), 65–75.

[31]For details, see Austriaco, "Pre-implantation Embryo."

[32]For an extensive discussion and critique of contemporary views denying the substantiality of living organisms, see J.P. Moreland and Scott B. Rae, *Body & Soul: Human Nature & the Crisis in Ethics* (Downers Grove, IL: Intervarsity Press, 2000), 17–228.

not build an organism. Rather, an organism is that living structure which is always in the process of developing. Human development does not end at birth or at even at adulthood as many people believe. It is now clear that aging is the natural and final step in animal development.[33] Development is a lifelong process of change, and the organism is the dynamic structure undergoing this change through time. This perspective allows one to see that calling the human organism an embryo, fetus, infant, teenager, or an adult is to arbitrarily label and distinguish certain segments of a continuous chain of developmental events which do not differ in kind. Each is a different manifestation of the same organism, the same living system, at a later stage of change. Once fertilization occurs, the living system does not require further information—from the systems view, genetically-encoded molecules that further specify the dynamic movement of the system—to complete development. In support of this holistic perspective, the axes of the embryo, the coordinate system which tells the embryo what is top, bottom, left and right, have now been implicated in establishing the axes of the fetus, suggesting that continuity exists between the one-cell embryo, the fetus, and therefore, the newborn.[34] In a related note, much effort has recently gone into trying to discern rationally those incontrovertible qualities or properties whose acquisition transforms a biological human being into a moral human being possessing moral status.[35] However, all of these attempts are bound to fail because they do not acknowledge the biological substantiality and continuity of the human organism made clear by the systems perspective. Thus, they end up falling into a dualistic anthropology which is philosophically untenable.[36] The most critical transformative event in the life cycle of any animal, indeed, the only rationally discernable and nonarbitrary event that makes it an animal, and in the case of the human organism, a person, is the cell-to-organism transition which occurs at fertilization.

Fourth, in recent years, some bioethicists have questioned the proposition that fertilization is that moment which properly marks the beginning of the organism, because scientists often define fertilization as a complex sequence of coordinated events which begins with sperm penetration and ends some hours or days later with the union of the pronuclei of the sperm and the egg.[37] In

[33]For details, see Richard Arking, *The Biology of Aging: Observations and Principles*, 2nd ed. (Sunderland, MA: Sinauer Associates, 1998).

[34]M. A. Ciemerych, D. Mesnard, and M. Zernicka-Goetz, "Animal and vegetal poles of the mouse egg predict the polarity of the embryonic axis, yet are nonessential for development," *Development* 127.16 (August 15, 2000): 3467–3474. For a review, see M. Zernicka-Goetz, "Patterning of the embryo: the first spatial decisions in the life of a mouse," *Development* 129.4 (February 15, 2002): 815–829.

[35]For instance, see Mary Anne Warren, *Moral Status: Obligations to Persons and Other Living Things* (Oxford: Clarendon Press, 1997).

[36]For discussion, see Patrick Lee, "Human Beings Are Animals," in *Natural Law and Moral Inquiry: Ethics, Metaphysics, and Politics in the Work of Germain Grisez*, ed. Robert P. George (Washington, D.C.: Georgetown University Press, 1998), 135–151.

[37]For an extended discussion of this view, see Ronald M. Green, *The Human Embryo Research Debates: Bioethics in the Vortex of Controversy* (Oxford: Oxford University Press,

response, 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. It can be compared to the toppling over of the first domino which begins the collapse of a branching chain of ten million dominoes. If one had to pick a biological event to correspond to this falling first domino, it is properly the entry of the sperm into the egg which leads to the explosion of intracellular calcium levels which triggers the reorganization of the egg's molecular network. Prior to this, the egg was a living system in stasis. After this, it is a different system undergoing change, change that can continue unhindered for a hundred years.[38]

Finally, some have suggested that the malleable nature of early embryogenesis has put into doubt the traditional understanding of the embryo. For instance, developmental biologists have noted that separate and genetically distinct embryos (which if human, might have gone on to become fraternal twins) can sometimes fuse during early development to form a single organism.[39] This study along with others demonstrating the totipotency of the cells of the blastocyst have been used to attack the individuality and substantiality of the early embryo, suggesting that an embryo does not come into being until it loses its "unstable" existence some hours or even days after sperm-egg fusion. First, note that this study involved cells manipulated using the techniques of IVF, and it is not clear if this particular type of embryonic fusion

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2001), 25–30. A similar argument is made by T.A. Shannon and A.B. Wolter in their "Reflections on the Moral Status of the Pre-embryo," *Theological Studies* 51.3 (December 1990): 606–608.

[38]Bioethicist Ronald Green has correctly noted that the egg emits chemoattractants, chemical signals which attract the sperm even before the sperm enters the fallopian tubes. This, he speculates, may therefore be the proper beginning of fertilization because here the sperm and egg come into "contact." See Green, *Human Embryo*, 27. From the systems perspective, Green's speculation is incorrect. Yes, interaction with the chemoattractants of the egg changes the behavior of the sperm, but fertilization properly marks the cell-to-organism transition which alters the systems dynamics of the molecules not in the sperm but in the *egg.* The egg is the critical gamete here, because it is the egg which in itself bears the molecular components necessary for axes specification, an essential component in the cell-to-organism transition. As cloning technology has demonstrated, the sperm is not necessary for this.

[39]L. Strain et al., "A true hermaphrodite chimera resulting from embryo amalgamation after in vitro fertilization," *New England Journal of Medicine* 338.3 (January 15, 1998): 166–169, quoted in Green, *Human Embryo*, 30. Also see the essay by Helen Pearson, "Dual Identities," *Nature* 417.6884 (May 2, 2002): 10–11.

happens naturally.[40] Nonetheless, as mentioned above, there is already clear evidence for the establishment of positional information of the embryo by sperm penetration, demonstrating that individuality is established at the earliest point of embryogenesis. The embryonic living system even if it is multicellular is one single system. Thus, studies like the one describing embryonic fusion are just further examples of the robustness of the human developmental program. In other words, from the systems perspective, the fusion of two embryos to produce a single organism can be described as the process of first breaking down one molecular network and then incorporating its molecular constituents into the network of another living system which absorbs them. An analogous situation occurs when one drops a cube of ice into a glass of water. Does this prove that the ice cube was not an individual entity? Empirical observations like the one described in the embryonic fusion study do not pose insurmountable obstacles to the dynamic and substantial view of the early human organism proffered by systems biology.

A Systems View of Stem Cells and Stem Cell Lines

We now turn to ontological questions raised by recent advances in biomedical research beginning with issues related to stem cell technology. Stem cells are cells that have the ability to divide indefinitely and to give rise to specialized differentiated cells as well as to new stem cells with identical potential. There are two basic types. Adult stem cells are stem cells derived from different origins in the adult organism (bone marrow, brain, and skeletal muscle, just to mention a few) which possess the remarkable ability to reprogram themselves and give rise to cell types of a radically different type.[41] For example, bone marrow stems cells have the ability to form differentiated muscle cells when they are introduced into X-chromosome-linked muscular dystrophy (mdx) mice.[42] Embryonic stem cells, on the other hand, are stem cells derived from the blastocyst, which is destroyed in the process.[43] These cells also have a remarkable developmental plasticity and have been used in mice to generate a wide variety of cell populations in vitro.[44] Since it is clear that the embryonic stem cell is the source for all the cell types of the mammalian organism, some

[40]Some indirect evidence does suggest that human chimeras may arise naturally though the mechanism which gives rise to these individuals is far from clear. See de la Chappelle et al., "Early fusion of two human embryos?" *Annals of Human Genetics* 38.1 (1974): 63–75; and W.R. Mayr, V. Pausch, and W. Schnedl, "Human chimaera detectable only by investigation of her progeny," *Nature* 277.5693 (1979): 210–211.

[41]For a comprehensive review, see G. Almeida-Porada, C. Porada, and E.D. Zanjani, "Adult Stem Cell Plasticity and Methods of Detection," *Reviews in Clinical and Experimental Hematology* 5.1 (March 2001): 26–41.

[42]E. Gussoni et al., "Dystrophin expression in the mdx mouse restored by stem cell transplantation," *Nature* 401.6751 (September 23, 1999): 390–394.

[43]For a recent review, see M.F. Pera, "Human pluripotent stem cells: a progress report," *Current Opinion in Genetics & Development* 11.5 (October 1, 2001): 595–599.

[44]For a review, see J. Rathjen and P.D. Rathjen, "Mouse ES cells: experimental exploitation of pluripotent differentiation potential," *Current Opinion in Genetics & Development* 11 (October 1, 2001): 587–594.

have contended that that it should therefore be considered an embryo.[45] But should it? As noted in the introduction, Harriet Rabb, legal counsel for then NIH director, Harold Varmus, concluded that it should not. With a clearer understanding of the nature of the embryo, we can now better evaluate her argument.

From the systems perspective, the stem cell is a cell and not an organism. Though the stem cell is like the embryo in that it does have the potential to generate all the tissue types of the human body, i.e., it is pluripotent, it does not have the potential to carry out the basic process of axis formation that establishes the animal's body pattern. In other words, the stem cell cannot produce the different cell types of the body in a sequential and ordered manner. Thus, its systems dynamics differs from that which characterizes the embryo. Rather, the stem cell is like a talented individual who can play any instrument in the orchestra but is unable to organize and coordinate all the musicians so that they will be able to play a symphony. One important study has demonstrated that stem cells can develop into an adult mouse, but these cells were first inserted into an abnormal tetraploid embryo.[46] As we have pointed out, however, axis formation is specified very early in embryogenesis, suggesting that the abnormal embryo could have provided the embryonic stem cells with the pattern to organize the animal's body plan. Thus, this scientific report does show that the stem cell is unlike any other somatic cell type in the body; but its inability to independently organize the cells in order to form the body of an animal demonstrates that it still remains a cell. The legal counsel was right.

At this point, we should discuss the often-misunderstood notion of potentiality, from the systems perspective. Both a stem cell and an embryo are potentially adult organisms, but they are not equivalent as some ethicists have argued.[47] As a living system undergoing developmental change, the embryo has an active potentiality for maturity. In other words, if left alone, the changing network of molecules undergoing a deterministic process will necessarily realize its potential and be transformed into a mature organism. Theoretically, one could model the embryo *in silico* and predict the adult organism which it will become simply because animal development as a deterministic system does not require any further input of information after fertilization. In a similar manner, an orchestra that has begun a symphony will complete the performance on its own accord. It has an active potentiality to complete the symphony, because with the score, all that is needed is in place to undertake its task. The stem cell on the other hand does not have this type of potential. It only has a passive potentiality to become an adult organism, a potentiality that requires the

[45]In a note to IVF researchers, John Catford, Director of Public Health of the Australian State of Victoria, stated: "Totipotent stem cells are considered equivalent to embryos, whether they arise from fertilization or nuclear transfer or any other means," quoted by N. Tonti-Filippini and P. McCullagh, "Embryonic Stem Cells and Totipotency," *Ethics & Medics* 25.7 (July 2000): 2.

[46]A. Nagy et al., "Derivation of completely cell culture-derived mice from early-passage embryonic stem cells," *Proceedings of the National Academy of Sciences* 90.18 (September 15, 1993): 8424–8428.

[47]See note 5 above.

input of information (in the form of other molecular components or interactions) in order to be realized. A group of ninety-six economists is potentially an orchestra in this sense. They would need additional training, additional information, in order to perform a symphony. As the study mentioned above demonstrated, the stem cell needs the context of an embryo to establish the pattern of the body. It is not self-sufficient, and modeling the system dynamics of a stem cell would not allow one to predict that it would necessarily become an adult organism. To further illustrate this distinction, we note that every eight-year-old child has an active potentiality to become a teenager—one could look at the child and say that he has to become a teenager because it is intrinsic to him—but only a passive potentiality to become a biologist or an economist or president of the United States. In like manner, only the embryo has an active potentiality to develop into an adult organism. The stem cell, like every other cell in the body, even with cloning technology, has only a passive potentiality for this same end.

A Systems View of Cloning

Until recently, fertilization was thought to be the only process known to be able to convert a mammalian egg into an organism. This dramatically changed with the announcement that a sheep named Dolly had been cloned in Scotland using a procedure called somatic cell nuclear transfer (SCNT).[48] In brief, SCNT involves the introduction of the nucleus of a somatic cell (a cell, neither an egg nor a sperm, that is usually derived from an adult organism) into an enucleated egg. It appears that the molecules in the cytoplasm of the egg are able to reprogram the nucleus obtained from the adult cell and initiate embryogenesis. Thus, if the product of SCNT is placed into the uterus of a foster female animal, it is able to develop into an adult organism.

How then are we to understand the ontological status of the product of somatic cell nuclear transfer? An unsigned opinion piece in the prestigious scientific journal *Nature* has recently suggested that the pro-life position that defines the beginning of human life as the union of sperm and egg has been undermined by cloning, since no fertilization event marks the origin of the life of a clone.[49] To support this stance, the commentary points out that cloning is so radically different from fertilization that the chair of one ethical advisory board has argued that an embryo created by SCNT is not a bona fide embryo and suggests instead that it be called an "ovasome."[50] The argument of this op-ed piece is flawed. It fails to recog-

[48]I. Wilmut et al., "Viable offspring derived from fetal and adult mammalian cells," *Nature* 385.6619 (February 27, 1997): 810–813. Dolly was actually not the first mammal to be cloned. She was the first mammal to be cloned using a nucleus from a differentiated cell obtained from an adult animal. In 1994, cloned calves had already been produced using nuclei isolated from embryos. See M. Sims and N.L. First, "Production of calves by transfer of nuclei from cultured inner cell mass cells," *Proceedings of the National Academy of Sciences* 91.13 (June 21, 1994): 6143–6147.

[49]Opinion, "The meaning of life," *Nature* 412.6844 (July 19, 2001): 255.

[50]Ann A. Kiessling, "In the stem-cell debate, new concepts need new words," *Nature* 413.6855 (October 4, 2001): 453.

nize that the pro-life position is based on the view that fertilization is significant not because it marks the beginning of life, per se, but rather because it effects a cell-to-organism transition. As we have seen, the systems perspective can clarify this argument by defining this transition as the transformation of both the structure and the dynamics of a living system that takes place when the gametes fuse. Fertilization is not the beginning of life, per se, since the egg as a cell is already alive, but it is the origin of life in a new form, the form of an organism. 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.

As a final comment, we should note that SCNT, as a technique, is older than Dolly. In 1984, thirteen years before the birth of the cloned sheep, experiments that involved the transfer of nuclei obtained from early embryonic cells into enucleated mouse embryos failed to demonstrate that these nuclei could support significant embryogenesis.[51] These "embryos," which were able to complete several cell divisions, some even becoming "blastocysts," died soon afterwards, and the authors of the study concluded that "the cloning of mammals, by simple nuclear transfer, is biologically impossible." The breakthrough with Dolly happened only because her creators specifically chose a nucleus obtained from a cell which had been cultivated in a culture containing few nutrients thus "starving" it into a dormant, noncycling state. Thus, it is not correct to simply say that SCNT effects the cell-to-organism transition, because the long history of failed attempts at cloning a mammal with SCNT suggests that is not easy to mimic fertilization. More precisely, we need to say that it is the particular SCNT procedure first developed by Ian Wilmut and his colleagues which is able to effect the cell-to-organism transition in mammals. The birth of Dolly is proof of this. Its SCNT predecessors on the other hand could not. Their failure to produce a single live birth is sufficient evidence. Consequently, the "clones" generated by these pre-Dolly procedures including the ones generated in 1984, even if they developed into blastocyst-like structures, were only pseudo-embryos. The significance of this will become more apparent in the discussion of parthenogenesis which follows.

A Systems View of Parthenogenesis

As we noted in the introduction, Cibelli et al. have claimed that the human parthenote they have produced is unlike the human embryo. From the systems perspective, the validity of their argument would depend upon whether their procedure

[51] J. McGrath and D. Solter, "Inability of mouse blastomere nuclei transferred to enucleated zygotes to support development in vitro," *Science* 226.4680 (1984): 1317–1319. For a comprehensive review of the history of mammalian cloning, see Davor Solter, "Mammalian Cloning: Advances and Limitations," *Nature Reviews Genetics* 1.3 (December 2000): 199–207.

of activating the human oocyte effected a bona fide cell-to-organism transition. In other words, was the human parthenote generated at ACT an embryo or a pseudo-embryo?

Our analysis is complicated by some confusion in the terminology. Classically, parthenogenesis has been defined as an alternative mode of reproduction. It was first described in the modern period by Charles Bonnet in 1740 when he noted in his book, *D'Aphids,* that female aphids could produce live young without prior fertilization. This phenomenon has also been observed in other species, notably in several kinds of New World lizards, where whole populations are composed entirely or almost entirely of genetically identical females.[52] Note that in these examples, it is clear that the parthenogenetically activated egg had undergone the cell-to-organism transition. The living clones, either of aphids or of lizards, are proof of this. However, today, the term "parthenogenesis" is also being used to describe the process whereby an egg is artificially activated to begin progressing through the early stages of embryogenesis. As we have already discussed, however, cellular progression through the early stages of embryogenesis is not sufficient proof that the cell-to-organism transition has taken place. The early pre-Dolly SCNT procedures indicated that it is hard to mimic fertilization. Though some of the "clones" which they generated were able to develop to a blastocyst-like stage, none of them survived. Every single one of these entities died, suggesting that the procedure which generated them did not give them the capability to complete development. Again, since abnormal dynamics points back to abnormal structure, these "clones" could not have been bona fide embryos. The question before us, therefore, is to determine whether the parthenogenetic activation of mammalian eggs done at ACT is akin to the SCNT procedure that was able to generate Dolly, or to one of its predecessors that was unable to effect the cell-to-organism transition.

There are many experimental procedures, mechanical, electrical, and chemical, which can artificially activate the mammalian egg so that it will begin to divide and develop in the absence of sperm.[53] What is significant, however, is that *none* of these activated mammalian eggs has ever survived the embryonic period.[54] Recently, an activated primate marmoset egg which developed into embryo-like structures comprising only of parthenogenetic cells was shown to be capable of implantation.[55] However, all these "embryos" soon died. Significantly, the first time parthenogenesis has "worked" in mammals occurred when a chimeric bovine embryo was reconstructed from cells derived from a parthenogenetically activated egg and an in

[52]For a review, see C.J. Cole and C.R. Townsend, "Parthenogenetic lizards as vertebrate systems," *Journal of Experimental Zoology*, Suppl 4 (1990): 174–176.

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

[54]For extensive discussion of this, see M.H. Kaufman, *Early Mammalian Development: Parthenogenetic Studies* (Cambridge: Cambridge University Press, 1983).

[55]V.S. Marshall, L.J. Wilton, and H.D.M. Moore, "Parthenogenetic Activation of Marmoset (*Callithrix jacchus*) Oocytes and the Development of Marmoset Parthenogenones In Vitro and In Vivo," *Biology of Reproduction* 59.6 (December 1998): 1491–1497.

vitro fertilized embryo.[56] The chimeric male calf which was born clearly had cells derived from the parthenote. Significantly, a human chimera of normal and parthenogenetic cells has also been described.[57] Both these studies suggest that cells derived from a normal mammalian embryo are necessary for the parthenote to develop into a mature organism—parthenogenetically activated mammalian eggs are in themselves unable to develop into mature animals. This is supported by reports which suggest that parthenogenetically activated eggs which develop in mammalian females, including human females, eventually develop into ovarian tumors called teratomas.[58]

Finally, we should note that there is a clear molecular basis for this developmental failure. All the experimental data to date suggest that, because of genomic imprinting, mammalian embryogenesis cannot occur in the absence of chromosomes derived from the paternal lineage.[59] In brief, genomic imprinting is the process whereby a handful of genes are inherited in a silent state—they are imprinted—from either one of the two parents. Thus, an egg which is artificially induced to develop parthenogenetically lacks the activity of all those genes which have been rendered silent in the mother's genome. Normally, these genes would be inherited in an active state from the paternal lineage, but these are absent in parthenogenesis. Mutations in these imprinted genes manifest themselves as parent-of-origin effects, where the effect of the mutation depends upon whether it was inherited from the paternal or the maternal line. Though the purpose of imprinting is not yet clear, it appears to play an important role in human development as there are human developmental disorders which arise from errors in imprinting.[60] More recently, a woman has been described who has a global disorder of imprinting in the female germ line.[61] Genes which normally carry a maternal imprinting pattern assume a paternal pattern in her "embryos," which were indistinguishable from a complete hydatidiform mole. In fact, it is thought that an error in genomic imprinting is also the cause for the abnormal development that leads to the mole.

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[56]A. Boediono et al., "Offspring Born from Chimeras Reconstructed from Parthenogenetic and In Vitro Fertilized Bovine Embryos," *Molecular Reproduction and Development* 53.2 (June 1999): 159–170.

[57]L. Strain et al., "A human parthenogenetic chimaera," *Nature Genetics* 11.2 (October 1995): 164–169.

[58]G.H. Lee et al., "Genetic dissection of susceptibility to murine ovarian teratomas that originate from parthenogenetic oocytes," *Cancer Research* 57.4 (1997): 590–593.

[59]For in-depth reviews, see both M.S. Bartolomei and S.M. Tilghman, "Genomic Imprinting in Mammals," *Annual Review of Genetics* 31 (1997): 493–525; and W. Reik and J. Walter, "Genomic Imprinting: Parental Influence on the Genome," *Nature Reviews Genetics* 2.1 (January 2001): 21–32.

[60]For a review, see M.L. Hanel and R. Wevrick, "The role of genomic imprinting in human developmental disorders: lessons from Prader-Willi syndrome," *Clinical Genetics* 59.3 (March 2001): 156–164.

[61]H. Judson et al., "A global disorder of imprinting in the human female germ line," *Nature* 416.6880 (April 4, 2002): 539–542.

In conclusion, from the systems perspective, all of the evidence, from both developmental and molecular biology, suggests that parthenogenetically activating a mammalian egg with the procedures described to date cannot effect the cell-to-organism transition. Thus, the human parthenote created at ACT could only have been a pseudo-embryo. This of course would mean that it is not a human being.[62]

A final, and maybe, obvious comment: If the human parthenote created at ACT is not a human being, then it does not have the moral status of the human embryo. Therefore, Cibelli et al. appear to be correct. Any experimental procedure involving the manipulation of their human parthenote—in fact, of any pseudo-embryo—should be morally permissible. This would include destroying the parthenote to harvest embryonic stem cells which could then be used for regenerative therapy. Putting the moral status of the parthenote aside for a moment, however, another moral objection to this therapeutic approach comes to mind. Many studies suggest that imprinted genes may affect the development and genesis of different tissues and organs. For instance, they probably have a role in brain development or function given the surprisingly large number of neurological and psychiatric disorders in which parent-of-origin effects are observed.[63] Given these studies, is it not reasonable to expect that any ES cells or tissues derived from human parthenotes would also be abnormal? Why then should we risk exposing patients to any further complications associated with abnormally imprinted embryonic stem cells or tissues, especially when regenerative medicine using adult stem cells would circumvent all these problems?[64]

Embryo or Pseudo-Embryo?

From the systems perspective, the critical question at the beginning of life is whether a cell or clump of cells has undergone the cell-to-organism transition. In other words, is it an embryo or a pseudo-embryo? Resolving this question will be-

[62]As Mark S. Latkovic has pointed out, it appears that the Magisterium of the Catholic Church presumes that human parthenogenesis *would* create a human being. See his essay, "The Science and Ethics of Parthenogenesis," *National Catholic Bioethics Quarterly* 2.2 (Summer 2002): 245. I would argue that this would be true if the Magisterium understood the term in its classical sense. As we have already noted, parthenogenesis, understood in this way, does involve the cell-to-organism transition. However, parthenogenesis understood simply as the artificial activation of an egg is different. It is not yet clear if future discoveries in developmental genetics will one day circumvent the need for imprinted genes in mammalian embryogenesis. At that point, parthenogenetic activation of a human egg would indeed create a human being.

[63]For a review, see A.R. Isles and L.S. Wilkinson, "Imprinted genes, cognition and behaviour," *Trends in Cognitive Sciences* 4.8 (August 2000): 309–318.

[64]Recently, a scientific group has reported the discovery of a rare adult stem cell in bone marrow which has properties that have until now only been associated with ES cells. These multipotent adult progenitor cells or MAPCs are immortal and pluripotent but, unlike embryonic stem cells, do not give rise to tumors. They appear to be the ideal cell type for regenerative or transplantation medicine. See Y. Jiang et al. "Pluripotency of mesenchymal stem cells derived from adult marrow," *Nature* 418.6893 (July 4, 2002): 41–49.

come increasingly difficult as scientists involved in reprogenetics continue manipulating different types of cells to generate new kinds of embryo-like entities. For instance, it has just been reported that studies are underway to look at aggregates of surviving mono-nucleated cells isolated from several nonviable human embryos on day three or day four after fertilization.[65] Are these embryos? The systems perspective proposes that any analysis that seeks to respond to questions of this type has to begin with the process itself and the experimental manipulations involved. Can this particular type of process or experimental procedure effect the cell-to-organism transition? Proof of this capacity would be one clear instance whereby a product generated by the process or procedure was able to develop to maturity. Fertilization (both in vivo and in vitro), somatic cell nuclear transfer involving a nucleus obtained from a starved, quiescent cell as done by Wilmut and colleagues, and parthenogenesis in nonmammalian animals are all processes which pass this standard. Each of these procedures has resulted in a self-sustaining, mature organism. Thus, in the absence of evidence to the contrary, it is reasonable to presume that any embryo-like entities generated by these processes are indeed bona fide embryos. However, continued research in developmental biology has also demonstrated that certain molecules are essential for normal development. The transcription factor *Oct-4* is an example of this. In the absence of molecules of this type, even processes known to effect the cell-to-organism transition are unable to do so. Thus, the products of these failed processes and procedures—the mole is the prime example—are pseudo-embryos with system structures and system dynamics unlike those that define the embryo and drive embryogenesis. Likewise, if a process or procedure has never successfully generated a mature organism, it is reasonable to conclude that it is unable to effect the cell-to-organism transition. Fertilization is not easy to mimic. Therefore, embryo-like entities generated by these procedures should also be properly called pseudo-embryos. Finally, we should note that the line that distinguishes an embryo and a pseudo-embryo can often be fuzzy because of our incomplete understanding of the genetics of human development. However, improved modeling of human development as a dynamic and deterministic process promises to clarify this picture.

Postscript: A Systems View of Hylomorphism

Though it may not be immediately apparent, the systems perspective articulated in this essay is an initial attempt to reappropriate the principles of classical hylomorphic theory in light of recent advances in the natural sciences. First proposed by Aristotle and developed by his disciples especially St. Thomas Aquinas, hylomorphism sought to explain the nature of things and the nature of their changes. In brief, for the Aristotelian tradition, all things—especially all living things—are substances composed of both a formal and a material principle. The form, also called the soul, constitutes every being as a specific kind of thing with specific

[65]M. Alikani, and S.M Willadsen, "Human blastocysts from aggregated mono-nucleated cells of two or more non-viable zygote-derived embryos," *Reproductive Biomedicine Online* 5.1 (July/August 2002): 56–58. Available at www.rbmonline.com/Article/656; accessed on May 27, 2002.

causal powers. In the biological realm, it gives the plant or the animal its stability, its unity, and its identity. It organizes the organism, determines its nature, and specifies its end. The matter, on the other hand, is the "stuff" out of which the organism is made. According to the hylomorphic theory, both matter and form are inseparable in material beings. Together both give rise to a stable substance.

Stable substances, however, often change. For the Aristotelians, change involved the replacement of form. This process happens in two ways corresponding to the two types of change evident in the world. First, there is substantial change which radically alters the identity of the thing. Substantial changes involve the replacement of one substantial form with another. Next, there is accidental change which only modifies a thing without changing its nature. This kind of change involves the replacement of one accidental form with another. Thus, according to hylomorphism, all change observable in nature can be accounted for by invoking the shuffling of forms.

But in the twenty-first century, how does one talk about the "soul" of an oak tree or the "form" of a panther? This task is particularly important for the Catholic tradition which defined *de fide* at the Council of Vienne in 1312 that that the human soul is the form of the body.[66] Systems theory offers one possible response. Like the hylomorphic perspective, the systems perspective is a substantial perspective. The organism is seen here as a single unified network of interacting molecules which is organized in a species-specific manner. Here, the whole is greater than the sum of the parts. A typical 70-kg man is made up primarily of oxygen (43 kg), carbon (16 kg), hydrogen (7 kg), nitrogen (1.8 kg), and calcium (1 kg).[67] However, what makes this typical man radically different from a 68.8-kg pile of these five elements is that in his case, the elements are organized and interact in a particular way, a species-specific way. Indeed, a snapshot of the human body at any point in time would reveal an intricate network of molecular interactions distributed in three-dimensional space. As we have already discussed, from the systems perspective, these molecular interactions which reflect the nature of the living being also direct it to its biological end. Thus, systems theory could easily envision the organism as informed matter, here defined as molecular matter organized in a species-specific configuration. This particular pattern, this organization of the molecules of the plant or the animal, would be a reflection of its soul.

However, how then do we account for change? If all change simply involves the rearrangement of atoms, does this mean that change can only be of the accidental variety? Not quite. As a dynamic system, the living organism can undergo two types of changes. First, there are changes which involve alterations in the basic developmental trajectory of the living system. The paradigmatic example discussed throughout this essay is the cell-to-organism transition that occurs at fertilization. Here the addition of new molecules derived from the paternal lineage alters both the

[66]*Catechism of the Catholic Church*, n. 365.

[67]Body composition data was obtained from *Report of the Task Group on Reference Man*, International Commission on Radiological Protection (New York: Oxford University Press, 1975).

structure and dynamics of the system that is the egg giving rise to a different network of molecular interactions. This would be one example of substantial change. However, there are also events which disrupt development eventually leading to the collapse of the living system. These could come from intrinsic factors—mutations like a deletion of *Oct-4*—or from extrinsic factors—environmental chemicals which poison the developing embryo. Both would interrupt the deterministic process that characterizes the living thing, leading to its death. This too would be an example of substantial change. In contrast, because it is a robust system, the living organism can tolerate many nonessential modifications like changes in height, mass, or color. As discussed in the section involving system-nondisruptive mutations, these changes would involve the addition or removal of molecules which only play a peripheral role in determining the developmental trajectory of the organism. The basic framework of development remains intact. This type of transformation would be the systems analog to hylomorphic accidental change. Thus, according to the systems perspective, all change observable in nature can be accounted for by invoking the shuffling, not of forms per se, but of molecular interactions within dynamic systems.

Finally, any discussion of hylomorphic theory in the context of embryogenesis would be incomplete without a consideration of the theory of delayed hominization. Much ink has been spilt over this issue.[68] Basically, is the human body ensouled at some time after conception as Aristotle and Aquinas believed? As we have already noted several times above, the systems perspective highlights the seamless unity of the developmental process which begins at the cell-to-organism transition effected either by fertilization or by SCNT and ends at the death of the organism. Once development begins, there simply is no place in a deterministic process of molecular reactions for the series of substantial changes called for by delayed hominization. Substantial change can only occur at the outset of development because the organization of the molecules which drives development and specifies the identity of the thing is established then. All change after this point has to be accidental. The theory of delayed hominization is simply not compatible with contemporary models of animal development.[69]

[68]For a fairly recent discussion of delayed hominization and further citations to the literature, see the exchange between Mark Johnson and Thomas A. Shannon: Mark Johnson, "Delayed Hominization," *Theological Studies* 56 (1995):743–763; and Thomas A. Shannon, "Delayed Hominization: A Response to Mark Johnson," *Theological Studies* 57 (1996): 731–734; Mark Johnson, "Delayed Hominization: A Rejoinder to Thomas Shannon," *Theological Studies* (1997) 708–714; and Thomas A. Shannon, "Delayed Hominization: A Further Postscript to Mark Johnson," *Theological Studies* 58 (1997) 715–717; and Mark Johnson, "The Moral Status of Embryonic Human Life and Moral Issues," in *What Is Man, O Lord? The Human Person in a Biotech Age: Proceedings from the Eighteenth Workshop for Bishops* (Boston: The National Catholic Bioethics Center, 2002).

[69]Jean Porter has argued that the theory of delayed hominization is grounded not in scientific but in philosophical principles which need to be reconciled with the modern scientific account of embryogenesis which undergirds the Church's teaching on the origin of the human person at conception. See her "Is the Embryo a Person? Arguing with the Catholic Traditions." *Commonweal,* February 8, 2002, 8–10. The systems perspective can go far in responding to this challenge. To begin, I would ask this question: In light of systems theory, what would it mean for matter to be predisposed to form?