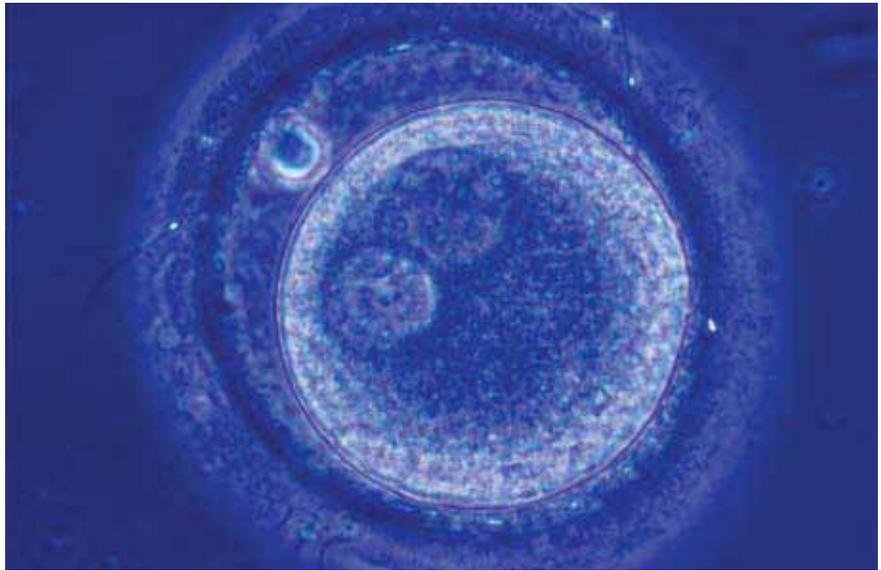


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When Does Human Life Begin?

A Scientific Perspective



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When Does Human Life Begin?

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When Does Human Life Begin?
A Scientific Perspective

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Cover Art

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The cover photograph shows a light micrograph of a cryopreserved, unicellular human zygote approaching syngamy. Human embryos, such as this one, are routinely created by *in vitro* fertilization in efforts at assisted reproduction, and are sometimes designated for research in which they are deliberately destroyed. Given the current state of biotechnology, most photos of human embryos in circulation today are made possible by these situations which of themselves are unnatural to human embryos. The Executive Director of the Westchester Institute, while authorizing the use of this photo, wishes to express his own moral objection to the *in vitro* production of human embryos.

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FOREWORD

It is really far past time to clear the air of the smog that obscures and confuses debates about abortion, embryonic research, cloning, and related issues.

Among the chief obfuscations and confusions is the claim that we do not know when human life begins. This frequently takes the form of claiming that the question is a matter of faith or religious belief. Nothing could be farther from the truth, as is lucidly and convincingly demonstrated in this White Paper.

When a human life begins is a question of science. The ethicist Peter Singer of Princeton University is famous, or notorious, for his advocacy of selective infanticide for babies who are born and then found to be defective in a way that makes them unwanted. Most people will find that argument morally abhorrent. But Singer is right about one thing. As he has said on many occasions, he and the pope are in complete agreement on when human life begins.

The debate in our society and others is not over when human life begins but is over at what point and for what reasons do we have an obligation to respect and protect that life. Before we can get to that argument, however, we need to clear the smog surrounding the question of when human life begins. This White Paper makes an invaluable contribution to that end.

It is sometimes said that the abortion debate is about “values” rather than “facts.” An honest debate about abortion, however, is about values based on facts. If we don’t get the facts right, we will not get our values right. Establishing by clear scientific evidence the moment at which a human life begins is not the end of the abortion debate. On the contrary, that is the point from which the debate begins.

Throughout history, there have been many societies that have decided that some human lives are more worthy of respect and protection than other human lives. While some such decisions are repugnantly racist, as in the case of Nazi Germany, or ideological, as in the case of Soviet and Maoist communism, others have made the decision on more sophisticated, even apparently humane, grounds. That is certainly true in the case of most of those who support an unlimited abortion license in our society. What we should not evade or obscure is the nature of the decision under discussion.

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Finally, Christians believe that all truth is one because God, who is the source and end of all truth, is one. On the question at hand, as on other questions, there is no tension, never mind conflict, between science and faith. Faith and science, when rightly understood, are in the service of truth. This White Paper is not an exercise in theology. Nor is it an exercise in ethics or moral reasoning. It is a scientific examination of facts which, when clearly understood, provide the subject matter upon which other forms of reasonable reflection—medical, moral, legal, political, and theological—can then be brought to bear. All who are involved in these debates should be grateful to the Westchester Institute for Ethics & the Human Person for providing this important clarification of what it is that we are debating.

Richard John Neuhaus
Editor in Chief
First Things

It is my great pleasure to introduce Dr. Maureen Condic's "When Does Human Life Begin?" as the first White Paper of the Westchester Institute for Ethics & the Human Person. Each contribution to this new White Paper series intends to offer a cogent and measured argument on a question of great moment, and Dr. Condic's inaugural paper provides us with nothing less.

Though human reason is not dependent upon biological findings for its certainty that a new human life wholly begins at some discrete moment, it is nonetheless dependent on the careful investigations of biologists like Dr. Condic to determine precisely where and when that discrete moment occurs.

In this White Paper, Dr. Condic challenges some of the conventional wisdom about that moment and argues that a coherent and non-arbitrary analysis of the scientific data forcibly points to the conclusion that a new human life commences at the precise moment when the membranes of the sperm and egg cells fuse. Specifically, she critiques the more common position that human life begins about 24 hours later during an event called syngamy (the breakdown of the two pronuclear membranes in the new cell, which results from the fusion of sperm and egg).

In this way, Dr. Condic accomplishes in the field of developmental biology exactly what the Westchester Institute hopes to foster in the realm of ethical reflection: namely, rigorous advancement of the discussion regarding unsettled questions of paramount moral concern.

With Dr. Condic's contribution, we are proud and delighted to launch our White Paper series.

Fr. Thomas Berg, L.C., Ph.D.
Executive Director
The Westchester Institute for Ethics & the Human Person

The Westchester Institute is profoundly grateful to Antoine Puech, whose generosity has made this publication possible.

INTRODUCTION

ACKNOWLEDGEMENT

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When Does Human Life Begin?
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Resolving the question of when human life begins is critical for advancing a reasoned public policy debate over abortion and human embryo research. This article considers the current scientific evidence in human embryology and addresses two central questions concerning the beginning of life: 1) in the course of sperm-egg interaction, when is a new cell formed that is distinct from either sperm or egg? and 2) is this new cell a new human organism—i.e., a new human being? Based on universally accepted scientific criteria, a new cell, the human zygote, comes into existence at the moment of sperm-egg fusion, an event that occurs in less than a second. Upon formation, the zygote immediately initiates a complex sequence of events that establish the molecular conditions required for continued embryonic development. The behavior of the zygote is radically unlike that of either sperm or egg separately and is characteristic of a human organism. Thus, the scientific evidence supports the conclusion that a zygote is a human organism and that the life of a new human being commences at a scientifically well defined “moment of conception.” This conclusion is objective, consistent with the factual evidence, and independent of any specific ethical, moral, political, or religious view of human life or of human embryos.

SUMMARY

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HOW HAS THE BEGINNING OF LIFE BEEN DEFINED?

The question of when human life begins is one of considerable ethical, legal, and political importance, particularly for public policy debates over abortion and embryonic stem cell research. Recently, a number of our nation's most prominent political leaders have weighed in on this question, proposing two very different sorts of answers. On the one hand, Nancy Pelosi, the Speaker of the House of Representatives, stated, "I don't think anybody can tell you when . . . human life begins."¹ Her sentiment has been echoed by Senator Biden,² who said that he believes life begins at conception, but that this is merely a religious opinion that could not legitimately be the basis for public policy. In contrast, Senator McCain has confidently stated that life begins "at the moment of conception,"³ although he did not offer a precise definition of when this moment occurs.

Modern science indicates that the beginning of life occurs sometime after the fertilization of an ovum by a sperm cell, yet fertilization itself is surprisingly difficult to define.

When in the course of prenatal development a new human being comes into existence is not an easy question to answer; indeed, it has been answered in many ways throughout history, based on the understanding of human development available at any given time. Advances in the study of human embryology have sharpened our focus to an increasingly narrow developmental time-frame. Modern science indicates that the beginning of life occurs sometime after the fertilization of an ovum by a sperm cell, yet fertilization itself is surprisingly difficult to define. The events immediately following the fusion of sperm and egg—and prior to the first cell division (an approximately 24-hour period also referred to as the first cell cycle)—have typically been viewed as part of the "process" of fertilization (see Figure 1, p. 17). At some point during this period, an embryo forms, but precisely when this occurs has been the subject of considerable disagreement and debate.

The point at which fertilization ends and embryonic development commences is commonly placed at "syngamy," the time when the membranes surrounding the nuclei derived from the sperm and the egg break down in preparation for the first cell division (see Figure 1E, p. 17). Indeed, many textbooks devoted to the topic of human embryology,⁴ as well as the legal codes of a number of countries⁵ and states within the USA,⁶ define the completion of fertilization and beginning of life in this manner. Yet this is not the only point at which life is said to begin. Recently,⁷ it has been asserted that the life and moral status of the embryo begin at the eight-cell stage, because zygotic transcription (the active utilization of embryonic genes) commences at this time; and prior to this moment, whatever is happening in the "fertilized egg"⁸ is being driven by maternal factors.⁹ Some push the onset of life to even later, to the formation of specific structures or the onset of specific developmental processes.¹⁰

¹ Nancy Pelosi, *Meet the Press* interview with Tom Brokaw, August 24, 2008. Transcript available at <http://www.msnbc.msn.com/id/26377338/page/3/> (accessed 9/12/2008; transcript on file with author).

² Joseph Biden, *Meet the Press* interview with Tom Brokaw, September 7, 2008. Transcript available at <http://www.msnbc.msn.com/id/26590488/page/4/> (accessed 9/12/2008; transcript on file with author).

³ John McCain, *Saddleback Presidential Forum* interview with Rick Warren, August 16, 2008. Transcript available at <http://transcripts.cnn.com/TRANSCRIPTS/080817/se.01.html> (accessed 9/12/08; transcript on file with author).

⁴ For example: "Fertilization is a complex sequence of coordinated events that begins with contact between a sperm and an oocyte . . . and ends with the intermingling of maternal and paternal chromosomes at metaphase of the first mitotic division of the zygote" [Keith L. Moore and T.V.N. Persaud, *The Developing Human*, 7th ed. (Philadelphia: Saunders-Elsevier, 2003), 31]; "At this point, [syngamy] the process of fertilization can be said to be complete and the fertilized egg is called a zygote" [Bruce M. Carlson, *Human Embryology and Developmental Biology*, 3rd ed. (Philadelphia: Mosby-Elsevier, 2004), 36].

⁵ International Consortium of Stem Cell Networks, "Global Regulation of Human Embryonic Stem Cell Research and Oocyte Donation" http://www.stemcellcentre.edu.au/PDF/Global_Regulation_HESC_Research_Oocyte_Donation.pdf (accessed October 6, 2008).

⁶ For example: VA. CODE ANN. § 20-156 (2004): "Embryo" means the organism resulting from the union of a sperm and an ovum from first cell division until approximately the end of the second month of gestation."

⁷ Phillip G. Peters, Jr., "The Ambiguous Meaning of Human Conception," *University of California-Davis Law Review* 40 (2006):199-228.

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8 Referring to the product of sperm-egg fusion as a “fertilized egg” is misleading; once an egg is fertilized, it ceases to be an egg. This term avoids the central question of what kind of cell is produced by fertilization.

9 There is good evidence from mouse and from human embryos that the zygotic genome becomes active before the first cell division: Luke Martin-McCaffrey et al., “RGS14 is a Mitotic Spindle Protein Essential from the First Division of the Mammalian Zygote,” *Developmental Cell* 7, no. 5 (November 2004): 763-9; Asangla Ao et al., “Transcription of Paternal Y-linked Genes in the Human Zygote as Early as the Pronucleate Stage,” *Zygote* 2, no. 4 (November 1994): 281-7; Robert Daniels et al., “XIST Expression in Human Oocytes and Preimplantation Embryos” *American Journal of Human Genetics* 61, no. 1 (July 1997): 33-9; Richard M. Schultz, “Regulation of Zygotic Gene Activation in the Mouse,” *Bioessays* 15, no. 8 (August 1993): 531-8; Christine Bouniol, Eric Nguyen, and Pascale Debey, “Endogenous Transcription Occurs at the 1-cell Stage in the Mouse Embryo,” *Experimental Cell Research* 218, no. 2 (May 1995): 57-62; Anthony T. Dobson et al., “The Unique Transcriptome Through Day 3 of Human Preimplantation Development,” *Human Molecular Genetics* 13, no. 14 (July 2004): 1461-70.

10 It is commonly claimed that life begins with the formation of the inner cell mass of the embryo (~four days post fertilization), or when the embryo implants in the uterus (~5-6 days post fertilization), or at the onset of gastrulation (~two weeks after fertilization).

The fact that life is truly a continuum further complicates the question of when a new life commences. Most human beings are produced from the union of two preexisting cells: sperm and egg. Sperm and egg cells were, in turn, generated from living cells that preceded them in the testes and ovaries, and so forth, back indefinitely to the beginning of all life. In light of the continuous nature of living cells, defining the beginning of a new organism as the onset of zygotic transcription or the breakdown of nuclear membranes is intellectually and scientifically unsatisfying. These are arbitrary points along a continuum of life—points that are likely to vary considerably across closely related species and across individuals of the same species. Such definitions are logically akin to linking the beginning of “personhood” to the eruption of teeth in an infant or to the onset of menses in an adolescent—they are arbitrary, variable, and not indicative of any fundamental change in the entity under consideration.

The continuum of cellular life—with living cells giving rise to new types of cells and, ultimately, to new individuals—has led some to conclude that the question of “when life begins” is unanswerable. Because cellular life exists in a continuum, this line of reasoning concludes, there can be no meaningful point at which a “new” human life is said to begin. Yet if this view is correct, we are left with a serious ethical dilemma: while no one objects to the destruction of ordinary human cells for biomedical research, the use of *human beings* for such purposes is universally condemned. Clearly, some non-arbitrary criteria must be established to determine when living human cells give rise to a new individual human being.

WHAT IS THE SCIENTIFIC BASIS FOR DISTINGUISHING DIFFERENT TYPES OF CELLS?

Science relies on detailed observation to determine when a change in cell type has occurred. Throughout embryogenesis, cells continuously change from one type to another, and these transitions can be reliably detected. Scientific distinctions are made between various cell types, based on two relatively simple criteria: cells are known to be different from each other because they have different composition (i.e., different genes are expressed, different proteins produced, etc.) and because they exhibit distinct types of cell behavior. For example, a transient embryonic population of cells, known as neural crest cells, produces a variety of different cell types during development, including the progenitors of all the sensory neurons of the body. As neural crest cells convert into this new cell type (sensory neural progenitors), they undergo a number of observable changes: they stop migrating, begin a period of more active cell proliferation, begin to express different genes, and assume a different cellular morphology. These changes are the basis for asserting that neural crest cells and sensory neural progenitors are *distinct* cell types.

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When cells are classified into specific types, differences in either composition or behavior are the bases for all *scientific*, as opposed to *arbitrary*, distinctions. If, for example, scientists were to propose that during embryonic development a novel cell type exists between a neural crest and a sensory neural progenitor cell, they would have to *prove* this assertion by pointing to specific material or behavioral characteristics that distinguish this cell both from the cell that gave rise to it and from the cell it subsequently generates—or risk having their assertions dismissed as mere fantasy.

In considering the question of when the life of a new human being commences, we must first address the more fundamental question of when a new cell, distinct from sperm and egg, comes into existence: when during the interactions of sperm and egg do we observe the formation of a new cell with both a material composition and a developmental pathway (i.e., a pattern of cell behavior) that are distinct from the cells giving rise to it? These two criteria (unique composition and behavior) are used throughout the scientific enterprise to distinguish one cell type from another—and if we reject them as the basis for making such distinctions, the only alternative is to make an essentially arbitrary decision.

HOW DOES THE ZYGOTE DIFFER FROM SPERM AND EGG?

The basic events of early development are both reasonably well characterized and entirely uncontested. Following the binding of sperm and egg to each other, the membranes of these two cells fuse, creating in this instant a single hybrid cell: the zygote or one-cell embryo (see Figure 1A). Cell fusion is a well studied and very rapid event, occurring in less than a second.¹¹ Because the zygote arises from the fusion of two different cells, it contains all the components of both sperm and egg, and therefore the zygote has a unique molecular composition that is distinct from either gamete.

Subsequent to sperm-egg fusion, events rapidly occur in the zygote that do not normally occur in either sperm or egg. The contents of what was previously the sperm, including its nucleus, enter the cytoplasm of the newly formed zygote. Within minutes of membrane fusion, the zygote initiates changes in its ionic composition¹² that will, over the next 30 minutes, result in chemical modifications of the zona pellucida, an acellular structure surrounding the zygote (Figure 1B). These modifications block sperm binding to the cell surface and prevent further intrusion of additional spermatozoa on the unfolding process of development. Thus, the zygote acts immediately and specifically to antagonize the function of the gametes from which it is derived; while the “goal” of both sperm and egg is to find each other and to fuse, the first act of the zygote is immediately to prevent any further binding of sperm to the cell surface. Clearly, then, the prior trajectories of sperm and egg have been abandoned, and a new developmental trajectory—that of the zygote—has taken their place.

Fig 1A Sperm-Egg Fusion

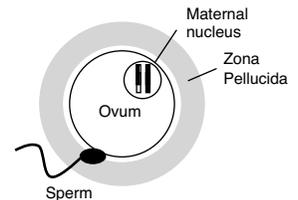


Fig 1B Zygote Formation

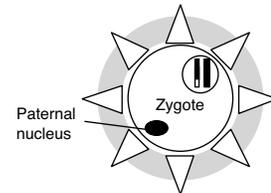


Fig 1C Early Acts of the Zygote

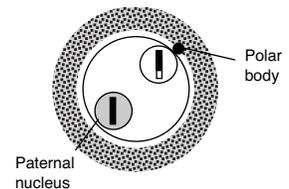
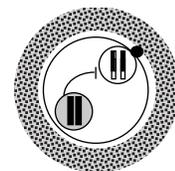


Fig 1D Onset of Zygotic Transcription



¹¹ Ulyana Vjugina and Janice P. Evans, “New Insights into the Molecular Basis of Mammalian Sperm-Egg Membrane Interactions,” *Frontiers in Bioscience* 13, no. 2 (January 2008): 462-76; Meital Oren-Suissa and Benjamin Podbilewicz, “Cell Fusion During Development,” *Trends in Cell Biology* 17, no. 11 (November 2007): 537-46.

¹² Llewellyn J. Cox et al., “Sperm Phospholipase C ζ from Humans and Cynomolgus Monkeys Triggers Ca²⁺ Oscillations, Activation and Development of Mouse Oocytes,” *Reproduction* 124, no. 5 (November 2002): 611-23; Christopher M. Saunders, Karl Swann, and F. Anthony Lai, “PLC ζ : A Sperm-Specific PLC and its Potential Role in Fertilization,” *Biochemical Society Symposia* 74 (2007): 23-36.

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13 See footnote 12.

14 The objection is commonly raised that for the first 30 minutes following sperm-egg fusion, the zygote is not “genetically unique” and therefore cannot be a new human individual. However, the transiently triploid genome of the zygote is entirely unique and distinct from that of either parent. Moreover, even the “definitive” genome present after 30 minutes continues to be altered in many ways during development (X-inactivation in females, elimination of DNA in B-lymphocyte maturation, epigenetic changes, etc.), without compromising the unique identity of the individual. The DNA eliminated at meiosis is not irrelevant to the subsequent development of the zygote. The unique pattern of development a zygote undergoes is not determined solely by the DNA, but also by other molecules present in the egg. Many genes important for development are transcribed during formation of the egg, and the proteins produced from these genes can influence zygotic development in important ways, even if the genes themselves are lost during meiosis.

Importantly, the brief “indeterminacy” of the zygotic genome is a problem for defining when a new individual comes into existence only if a unique diploid genome is definitional of an individual human being — that is, if the unique genome is both necessary and sufficient for a human being to be present. Although this kind of “DNA essentialism” seems highly intuitive to many, it is profoundly inadequate as a basis for determining whether a unique individual exists. If a unique human genome defines a human being, then identical twins are a single person, not two individuals. Similarly, if my unique DNA is definitional of me, then my body is an aggregate, and every cell in my body is a unique human being—a clone of me. Finally, cells removed from my body and maintained in the laboratory are also in possession of my unique genome and must also be clones of me, deserving of all rights and respect conferred upon me as a human being. Based on these few examples, it is clear that possession of a unique human genome is neither necessary (as in the case of identical twins) nor sufficient (as in the case of isolated cells) to define a unique human being.

15 Benjamin Loppin et al., “The Histone H3.3 Chaperone HIRA is Essential for Chromatin Assembly in the Male Pronucleus,” *Nature* 437, no. 7063 (October 27, 2005): 1386-90; Godfried W. van der Heijden et al., “Asymmetry in Histone H3 Variants and Lysine Methylation Between Paternal and Maternal Chromatin of the Early Mouse Zygote,” *Mechanisms of Development* 122, no. 9 (September 2005): 1008-22; Godfried W. van der Heijden et al., “Sperm-Derived Histones Contribute to Zygotic Chromatin in Humans,” *BMC Developmental Biology* 31, no. 8 (March 2008): 34.

16 Helen Fulka et al., “DNA Methylation Pattern in Human Zygotes and Developing Embryos,” *Reproduction* 128, no. 6 (December 2004): 703-8; Fatima Santos et al., “Dynamic Reprogramming of DNA Methylation in the Early Mouse Embryo,” *Developmental Biology* 241, no. 1 (January 2002): 172-82; Nathalie Beaujean et al., “Non-Conservation of Mammalian Preimplantation Methylation Dynamics,” *Current Biology* 14, no. 7 (April 2004): R266-7.

Within the first 30 minutes following sperm-egg fusion, the maternally derived nucleus completes its final round of meiotic division (Figure 1C), a process initiated by factors contributed by the sperm.¹³ Thus, for a brief time, the zygote is a triploid cell, containing one set of DNA from the sperm and two sets of DNA from the oocyte. The completion of meiosis in the maternally derived nucleus converts this triploid cell to a diploid state and establishes the definitive (i.e., final) genome of the zygote.¹⁴ By eliminating half of the maternally contributed DNA, the zygote acts in the interest of its own subsequent development to establish a genetic state that is dissimilar to that of gametes and uniquely capable of supporting continued embryonic development.

Following completion of meiosis, the maternally and paternally derived nuclei undergo rapid structural and chemical changes. Beginning within 30 minutes, protamine associated with the paternally derived DNA is replaced by histone,¹⁵ generating a “paternal” nucleus that is actually a hybrid of paternally derived DNA and maternally derived protein (Figure 1C). Substitution of histone for protamine is required for DNA replication and zygotic transcription, processes that will not commence for several hours. Thus, modification of the paternal nucleus anticipates the subsequent steps of zygotic development and can be understood only as part of an ongoing development that is unique to the zygote and distinct from that of sperm and egg. Moreover, the observation that maternally derived proteins bind to and alter the function of both egg- and sperm-derived DNA indicates that molecular interactions between the maternally and paternally derived components of the zygotic genome commence almost immediately after sperm-egg fusion.

Within the first hour following sperm-egg fusion, the DNA of both pronuclei is demethylated, but the paternally derived nucleus is more rapidly and extensively modified¹⁶ (Figure 1C). Demethylation is required for normal patterns of gene expression to occur when zygotic transcription begins approximately ten hours later, and it is, therefore, also part of a developmental sequence that is initiated by sperm-egg fusion and unique to the zygote.

Within 8-10 hours following sperm-egg fusion, both the maternally and paternally derived nuclei replicate their DNA in anticipation of the first round of cell division, which will not occur for another 15 hours¹⁷ (Figure 1D). The timing of the onset of DNA replication depends on factors from the sperm,¹⁸ again indicating that maternally and paternally derived components of the zygote are interacting to generate a coordinated pattern of development well before the end of the first cell cycle.

Immediately following the period of DNA replication, transcription begins in both halves of the genome¹⁹ (Figure 1D). Development beyond the two-cell stage critically depends on expression of zygotic genes,²⁰ indicating that even at the one-cell stage, the zygote is directing its own development. Interestingly, at this early stage, expression of maternally derived genes is actively blocked by the male pronucleus; transcription of the paternally derived DNA is four- to five-fold greater than that of

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maternally derived DNA.²¹ This differential transcription again indicates that the two halves of the genome interact prior to syngamy, even though they are located in physically separate compartments within the zygote.

Gradually, the two pronuclei move towards the center of the cell, in preparation for the first cell division (i.e., mitosis) of the zygote (Figure 1E). Immediately prior to cell division, syngamy occurs. Although syngamy is often characterized as the “uniting” of the two halves of the genome to generate a single diploid nucleus, in fact, syngamy is little more than the breakdown of the nuclear membranes that separate the two pronuclei. No “single” nucleus is formed at this point since there is no nucleus at all. The maternally and paternally derived chromosomes are merely present in the same general region of the cytoplasm. This physical co-localization is required for accurate segregation of the chromosomes during cell division, so that both cells of the two-cell embryo inherit identical DNA. Following nuclear membrane breakdown (i.e., “syngamy”), the first mitotic division of the zygote takes place, thus completing the first cell cycle and generating the two-cell embryo (Figure 1F).

From this time forward, although many complex interactions will occur between cells as the mature body is gradually produced, on the intracellular level DNA replication and cell division will proceed in more or less the standard way that is common to all body cells. Thus, the events of the first cell cycle, which modify the DNA contributed by sperm and egg to enable the participation of this DNA in embryonic development, are unique to the zygote and to the first cell cycle (i.e., the first day following sperm-egg fusion).

Based on this factual description of the events following sperm-egg binding, we can confidently conclude that a new cell, the zygote, comes into existence at the “moment” of sperm-egg fusion, an event that occurs in less than a second. At the point of fusion, sperm and egg are physically united—i.e., they cease to exist as gametes, and they form a new entity that is materially distinct from either sperm or egg. The behavior of this new cell also differs radically from that of either sperm or egg: the developmental pathway entered into by the zygote is distinct from both gametes. Thus, sperm-egg fusion is indeed a scientifically well defined “instant” in which the zygote (a new cell with unique genetic composition, molecular composition, and behavior) is formed.

IS THE ZYGOTE MERELY A NEW HUMAN CELL OR IS IT A NEW HUMAN INDIVIDUAL?

The events immediately following sperm-egg fusion provide incontrovertible evidence that a new human cell, the zygote, is produced by this event. Yet, these observations do not address whether the life of a new human individual has commenced. Is the zygote merely a new kind of cell, or is it a new *human being*—a distinct, individual human organism?

17 Gemma Capmany et al., “The Timing of Pronuclear Formation, DNA Synthesis and Cleavage in the Human 1-cell Embryo,” *Molecular Human Reproduction* 2, no. 5 (May 1996): 299-306.

18 Pierre Comizzoli et al., “Onset of the First S-phase is Determined by a Paternal Effect During the G1-phase in Bovine Zygotes,” *Biology of Reproduction* 62, no. 6 (June 2000): 1677-84; J. Schabronath and K. Gärtner, “Paternal Influence on Timing of Pronuclear DNA Synthesis in Naturally Ovulated and Fertilized Mouse Eggs,” *Biology of Reproduction* 38, no. 4 (May 1988): 744-9.

19 See footnote 9.

20 Toshio Hamatani et al., “Dynamics of Global Gene Expression Changes During Mouse Preimplantation Development,” *Developmental Cell* 6, no. 1 (January 2004): 117-31; Toshio Hamatani et al., “Global Gene Expression Profiling of Preimplantation Embryos” *Human Cell* 19, no. 3 (August 2006): 98-117. See also Diane M. Worrad, Prahlad T. Ram, and Richard M. Schultz, “Regulation of Gene Expression in the Mouse Oocyte and Early Preimplantation Embryo: Developmental Changes in Sp1 and TATA Box-binding Protein, TBP,” *Development* 120, no. 8 (August 1994): 2347-57, and references therein.

21 Fugaku Aoki, Diane M. Worrad, and Richard M. Schultz, “Regulation of Transcriptional Activity During the First and Second Cell Cycles in the Preimplantation Mouse Embryo,” *Developmental Biology* 181, no. 2 (January 1997): 296-307; Marie Wiekowski, Miriam Miranda, and Melvin L. DePamphilis, “Requirements for Promoter Activity in Mouse Oocytes and Embryos Distinguish Paternal Pronuclei from Maternal and Zygotic Nuclei,” *Developmental Biology* 159, no. 1 (September 1993): 366-78; Pierre G. Adenot et al., “Differential H4 Acetylation of Paternal and Maternal Chromatin Precedes DNA Replication and Differential Transcriptional Activity in Pronuclei of 1-cell Mouse Embryos” *Development* 124, no. 22 (November 1997): 4615-25.

Fig 1E Syngamy

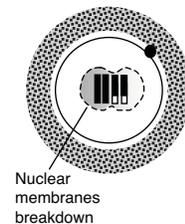
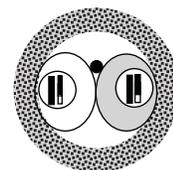


Fig 1F Two-Cell Embryo



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²² <http://www.merriam-webster.com/dictionary/organism> (accessed 10/1/2008; definition on file with the author). The second definition is also given verbatim by the National Library of Medicine, administered by the National Institutes of Health (<http://www.nlm.nih.gov/medlineplus/mpldictionary.html>).

The question of precisely when a new human organism comes into existence wasn't a matter of practical importance until the advent of *in vitro* fertilization and human embryo research. Consequently, scientists, philosophers, and bioethicists have not considered this question in great detail until recently; and appealing to experts (embryologists and ethicists alike) yields a plethora of opinions, often with very little factual evidence to support them. To address this question based on the scientific evidence, it is important to distinguish clearly between human cells and human organisms.

An organism is defined as “(1) a complex structure of interdependent and subordinate elements whose relations and properties are largely determined by their function in the whole and (2) an individual constituted to carry on the activities of life by means of organs separate in function but mutually dependent: a living being.”²² This definition stresses the interaction of parts in the context of a coordinated whole as the distinguishing feature of an organism.

The key feature of a human pattern of development is its organization towards the production of a mature human body.

²³ Maureen L. Condic and Samuel B. Condic, “Defining Organisms by Organization,” *National Catholic Bioethics Quarterly* 5: 331-353.

²⁴ Maureen L. Condic, “Life: Defining the Beginning by the End,” *First Things* 133: 50-54.

Based on this definition, it has been proposed that human beings (including embryonic human beings) can be reliably distinguished from human cells using the same kinds of criteria scientists employ to distinguish different cell types: by examining their composition and their pattern of behavior.²³ A human being (i.e., a human organism) is composed of characteristic human parts (cells, proteins, RNA, DNA), yet it is different from a mere collection of cells because it has the characteristic behavior of an organism: it acts in an interdependent and coordinated manner to “carry on the activities of life.” In contrast, collections of human cells are alive and carry on the activities of cellular life, yet fail to exhibit coordinated interactions directed towards any higher level of organization. Collections of cells do not establish the complex, interrelated cellular structures (tissues, organs, and organ systems) that exist in a whole, living human being. Similarly, a human corpse is not a living human organism, despite the presence of living human cells within the corpse, precisely because this collection of human cells no longer functions as an integrated unit.²⁴

Is a human zygote a human organism? For developing humans, the behavior and structures associated with adult stages of life are not yet fully manifest (embryos neither look like nor act like mature human beings). However, developing human beings are composed of characteristic human parts and they exhibit a *human* pattern of developmental behavior. *The key feature of a human pattern of development is its organization towards the production of a mature human body.*

From the moment of sperm-egg fusion, a human zygote acts as a complete whole, with all the parts of the zygote interacting in an orchestrated fashion to generate the structures and relationships required for the zygote to continue developing towards its mature state. Everything the sperm and egg do prior to their fusion is uniquely ordered towards promoting the binding of these two cells. Everything the zygote does from the point of sperm-egg fusion onward is uniquely ordered to *prevent* further binding of sperm and to promote the preservation and development of the zygote itself. The zygote acts immediately and decisively to initiate a program of development that will, if uninterrupted by accident, disease, or external intervention, proceed seamlessly through formation of the definitive body, birth, childhood, adolescence, maturity, and aging, ending with death. This coordinated behavior is the very hallmark of an organism.

Mere human cells, in contrast, are composed of human DNA and other human molecules, but they show no global organization beyond that intrinsic to cells in isolation. A human skin cell removed from a mature body and maintained in the laboratory will continue to live and will divide many times to produce a large mass of cells, but it will not re-establish the whole organism from which it was removed; it will not regenerate an entire human body in culture. Although embryogenesis begins with a single-cell zygote, the complex, integrated process of embryogenesis is the activity of an organism, not the activity of a cell.

Based on a scientific description of fertilization, fusion of sperm and egg in the “moment of conception” generates a new human cell, the zygote, with composition and behavior distinct from that of either gamete. Moreover, this cell is not merely a unique human cell, but a cell with all the properties of a fully complete (albeit immature) human organism; it is “an individual constituted to carry on the activities of life by means of organs separate in function but mutually dependent: a living being.”²⁵

WHY ISN'T SYNGAMY THE BEGINNING OF A NEW HUMAN LIFE?

Syngamy, the breakdown of nuclear membranes in preparation for cell division, is commonly held to be the point at which the zygote is formed and life begins. This definition does not deny that a new cell with unique composition and behavior is formed at sperm-egg fusion (a “pre-zygote,” perhaps), but it fails to specify the nature of this cell. The reasons for identifying syngamy as the beginning of life are two-fold. First, syngamy is the last event associated with the first cell cycle and thus represents the completion of this unique period of development. After this point, many interesting and complex interactions occur, but the cells of the embryo behave in manners that are also seen in other, more mature body cells. Thus, according to some, syngamy marks the end of the “process” of fertilization and the onset of a developmental trajectory driven by the zygote itself. Second, many believe that syngamy represents

²⁵ See footnote 22.

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the “fusion” of the maternally and paternally derived half-genomes, and the generation of the mature, diploid genome that is unique to the new individual. Both of these assertions are scientifically inaccurate.

Compared with the changes in both material composition and developmental trajectory that occur at the fusion of sperm and egg, syngamy is fundamentally an arbitrary definition for the beginning of life.

26 A good analogy for the communication between the maternally and paternally derived halves of the genome is the communication of two Internet-linked computers with different data sets that are executing a common program. The computers will transmit information and mutually modify each other's function via electronic signals that are carried by data cables or telephone lines. The mechanism of this indirect communication will not be substantially different for computers separated by a few feet than for those separated by a few thousand miles; computers located in the same room are not somehow more “united” by virtue of their physical proximity than are computers located in different countries. Similarly, DNA communicates indirectly and remotely via DNA-binding proteins, and this communication is not dependent on physical proximity. So long as the two halves of the genome are contained within a single cell (i.e., there is a common mechanism for communication between different elements of the genome), interaction between maternally and paternally derived DNA happens indirectly through transcription and translation of DNA binding proteins, mechanisms that do not require the DNA to be “united” within a single nuclear membrane.

27 Wolfgang Mayer et al., “Spatial Separation of Parental Genomes in Preimplantation Mouse Embryos,” *Journal of Cell Biology* 148, no. 4 (February 21, 2000): 629-34; Seungeun Yeo et al., “Methylation Changes of Lysine 9 of Histone H3 During Preimplantation Mouse Development,” *Molecules and Cells* 20, no. 3 (December 2005): 423-8; Fatima Santos et al., “Dynamic Reprogramming of DNA Methylation in the Early Mouse Embryo,” *Developmental Biology* 241, no. 1 (January 2002): 172-82; Jacqueline Bomar et al., “Differential Regulation of Maternal and Paternal Chromosome Condensation in Mitotic Zygotes,” *Journal of Cell Science* 115, no. 14 (July 15, 2002): 2931-40.

Compared with the changes in both material composition and developmental trajectory that occur at the fusion of sperm and egg, syngamy is fundamentally an arbitrary definition for the beginning of life. From a biological perspective, the breakdown of nuclear membranes at syngamy is a relatively mundane event along an *already progressing* developmental trajectory. The material composition of the cell does not change from the instant prior to syngamy to the instant after it takes place. There is no substantive change in the behavior of the cell at syngamy; all the preparations for cell division (DNA replication, assembly of the mitotic spindle, chromatin condensation) are already underway as the pronuclei move together. Indeed, nuclear membrane breakdown is not a unique, “zygote-forming” event, but rather it is part of every round of cell division that occurs through life. The zygote is the same cell—and it continues doing exactly what it was doing (i.e., preparing to undergo cell division) both before and after the pronuclei come into physical proximity. The developmental program observed during the first cell cycle (including the breakdown of nuclear membranes at syngamy) is clearly initiated by the fusion of the sperm and egg, and it progresses seamlessly from that instant forward.

The assertion that the mature, diploid genome forms at syngamy is also scientifically untenable. The definitive diploid genome is formed at the completion of meiosis. As detailed above, although syngamy appears to result in the “fusion” of the two pronuclei, the maternally and paternally derived DNA interact extensively prior to syngamy. The physical proximity of the two halves of the genome achieved after nuclear membrane breakdown is biologically irrelevant to the ongoing interaction of the DNA contained within the genome.²⁶ Moreover, the “mingling” of the DNA that occurs at syngamy is in some ways quite superficial. There is good evidence that full mingling of the maternal and paternal DNA strands is not completed during the first cell cycle, but rather that chromatin derived from each parent occupies distinct domains within the nucleus until at least the four-cell stage.²⁷ Thus, syngamy does not fully establish the normal state of a diploid nucleus (as is seen in mature somatic cells, with random mixing of DNA strands derived from both parents), further compromising syngamy as a definition of when the life of a new individual begins.

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The essential problem with the view that life begins at syngamy is the notion that a cell can change from one type (a “pre-zygote” that exists following sperm-egg fusion but prior to syngamy) into another type (the zygote that exists after syngamy) without any actual change in the material state or behavioral trajectory of the cell. This argument is simply not consistent with the scientific method. To assert that life begins at syngamy is to propose some form of mysticism: although a zygote cannot be distinguished in any significant manner from the “pre-zygote” that precedes it, the cell is now a zygote simply because one asserts that it is.

Regardless of how intuitively plausible syngamy may seem as a marker for the onset of a new cell (the zygote), without a demonstrable change in the material and/or the behavioral state of the cell—that is, without credible scientific *evidence* that a new cell type comes into existence at this point—one simply cannot assert that syngamy marks the beginning of a new human cell type, much less a new human being.

WHAT ARE PARTHENOTES, HYDATIDIFORM MOLES, AND CLONES?

Defining the beginning of life as the point at which a new, single-cell organism with unique composition and behavior is formed raises concerns about a number of entities that appear to be closely related to embryos. In particular, parthenotes, hydatidiform moles, and human clones raise issues that need to be carefully considered.

Cloning presents a challenge to the proposed definition of when life begins because cloning does not involve the union of sperm and egg.

In many animal species, mature egg cells can be induced to divide in the absence of sperm by external administration of an electrical pulse or a chemical stimulus that mimics some aspects of fertilization. Depending on the species, such “parthenotes” will progress through a sequence of developmental events that are quite similar to the development of a zygote. Indeed, in some species of animals, parthenotes occur spontaneously and can mature to fully formed adults.²⁸ However, for most species, including all mammals thus far studied, parthenotes do not develop normally or survive to birth.

Are parthenotes organisms? In the case of mammals, although parthenotes are similar to zygotes in certain respects, there are significant differences. Parthenotes contain only maternal chromosomes and, therefore, have a composition that is distinct from a zygote. Importantly, there is no strong evidence that human parthenotes exhibit globally coordinated activity of parts to generate an integrated pattern of development.²⁹ The fact that certain aspects of early zygotic behavior can be mimicked

²⁸ Christoph Vorburger, “Geographic Parthenogenesis: Recurrent Patterns Down Under,” *Current Biology* 16, no. 16 (August 22, 2006): R641-3; Robert G. Edwards, “The Significance of Parthenogenetic Virgin Mothers in Bonnethead Sharks and Mice,” *Reproductive BioMedicine Online* 15, no. 1 (July 2007): 12-5; T. V. Groot, E. Bruins, and J. A. Breeuwer, “Molecular Genetic Evidence for Parthenogenesis in the Burmese Python, Python Molurus Bivittatus,” *Heredity* 90, no. 2 (February 2003): 130-5; G. Cassar, T. M. John, and R. J. Etches, “Observations on Ploidy of Cells and on Reproductive Performance in Parthenogenetic Turkeys,” *Poultry Science* 77, no. 10 (October 1998): 1457-62.

²⁹ See discussion of human parthenogenesis in Mahendra Rao and Maureen L. Condic, “Alternative Sources of Pluripotent Stem Cells: Scientific Solutions to an Ethical Dilemma,” *Stem Cells and Development* 17, no. 1: 1-10.

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30 The question of whether human parthenotes can, in rare cases, exhibit an organismal pattern of development remains controversial, mostly due to a lack of rigorous scientific observation. While it is clear that human parthenotes do not develop normally, considerable caution is in order. Although stimulated egg cells do not differ in molecular composition from unstimulated eggs, they *do* exhibit a radical change in developmental trajectory—or behavior. Should it be demonstrated that parthenotes have some degree of coordinated development, it would raise the concern that they may be severely defective human organisms.

31 Andrew J. French et al., “Development of Human Cloned Blastocysts Following Somatic Cell Nuclear Transfer with Adult Fibroblasts,” *Stem Cells* 26, no. 2 (February 2008): 485-93.

32 In cases where the development of the cell produced by cloning is abnormal or where the clone does not survive, interpreting the nature of the cell produced by SCNT is problematic. If such clones exhibit any degree of normal, “organismal” coordination, caution would dictate they should be considered defective organisms.

artificially in the laboratory by delivering electrical or chemical stimulation to an oocyte in no way compromises the account of when life begins during the interaction of sperm and egg. An electrically stimulated egg is different in material composition from a bona fide zygote, and (on a molecular level) its “behavior” shows it to be quite distinct from a zygote.³⁰

A parallel, yet opposite case is presented by complete hydatidiform moles, a type of tumor that arises as a consequence of abnormal fertilization. Most commonly, hydatidiform moles form when a normal sperm fertilizes an oocyte that has abnormally lost its own genetic material. This event results in a tumor-forming cell with only paternally derived chromosomes. Hydatidiform moles grow quite rapidly and in some ways mimic a normal pregnancy (indeed, they are often referred to as a “molar pregnancy”). However, because hydatidiform moles contain only paternally derived chromosomes, they are distinguishable from zygotes based on their molecular composition. Moreover, hydatidiform moles behave quite differently from embryos: they grow as a chaotic mass of disorganized cells and tissues, all of which are unrelated to each other or to anything resembling a whole. Despite the fact that hydatidiform moles are generated from human gametes, they do not exhibit an embryonic pattern of organization or molecular composition; they are a collection of human cells, but not a human organism.

Finally, cloning, or somatic cell nuclear transfer (SCNT), presents a challenge to the proposed definition of when life begins because cloning does not involve the union of sperm and egg. In SCNT, the nucleus of an egg is removed and a mature body (somatic) cell is then fused to the empty egg, generating a hybrid cell that contains the genetic information of the body cell. In rare cases (usually less than one in a hundred transfers) the body cell nucleus is reprogrammed by the egg cytoplasm to a state that is capable of supporting a relatively normal pattern of embryonic development. Although human cloning has only recently been reported,³¹ it is likely that improvements in the cloning technique will enable human clones to be reliably generated through SCNT.

Does generation of a cloned human embryo or live human baby by SCNT compromise the definition of when a life begins? No. Upon transfer of a somatic nucleus to an empty egg cell, a new cell is generated that has a material composition and a developmental trajectory different from those of either of the two cells that produced it. In the rare cases where this hybrid cell goes on to produce a normal pattern of development, its behavior demonstrates that it is an organism.³² The production of human embryos via cloning indicates that although gametes are naturally disposed to generate a new organism upon fusion, embryos can also be generated under other, highly artificial circumstances. Cloning simply indicates that there is more than one way to make a zygote; it does not alter the analysis of natural fertilization or compromise our ability to determine precisely when fertilization results in an organism that is both materially and behaviorally distinct from the gametes that give rise to it.

DOES A HUMAN BEING CONTROL ITS OWN DEVELOPMENT OR IS IT “MANUFACTURED”?

Why has it been so difficult to define when a human life begins? Why has the view that life begins at syngamy (or at even later developmental stages) been so compelling for so many scientists and physicians? Those who advocate syngamy as the beginning of life appear to find it intuitively obvious that syngamy completes the unique events of the first cell cycle and produces “full union” of the gametes; until syngamy occurs, the “process” of fertilization is still underway. Those who advocate an even later point for the onset of life do so on the basis of a similar argument: the embryo has not yet fully formed until specific structures or processes are in place; until these “defining” events occur, the process of fertilization (or of embryo formation) is still underway. Clearly, if fertilization is seen as a process rather than as an event, then prior to the completion of this process the zygote is not yet fully present. Based on this view, the cell that results from the fusion of sperm and egg is not a new individual but, as expressed recently by a colleague, merely “a unique human cell in the process of becoming a new human, but not there yet.”³³

This way of thinking about human development is compelling to many because it is similar to our thinking about the much more familiar process of manufacturing. A car is not a car until it rolls off the assembly line—until then it is a bunch of parts in the process of becoming a car, but not there yet. Similarly, a cake is not a cake until it comes out of the oven—until then it is a variously gooey mass of flour, sugar, eggs, and butter that is gradually becoming a cake.

The embryo is not something that is being passively built by the process of development, with some unspecified, external “builder” controlling the assembly of embryonic components. Rather, the embryo is manufacturing itself.

However, a profound difference exists between manufacturing and embryonic development. The difference is who (or what) is doing the “producing.” The embryo is not something that is being passively built by the process of development, with some unspecified, external “builder” controlling the assembly of embryonic components. Rather, *the embryo is manufacturing itself*. The organized pattern of development doesn’t produce the embryo; it is produced *by* the embryo as a consequence of the zygote’s internal, self-organizing power. Indeed, this “totipotency,” or the power of the zygote both to generate all the cells of the body and simultaneously to organize those cells into coherent, interacting bodily structures, is the defining feature of the embryo.³⁴

³³ Micheline Mathews-Roth, M.D., Harvard University (personal communication).

³⁴ Identical twins demonstrate that totipotency may be preserved in all the cells of a human embryo, up to the two-cell stage, or even later (identical quintuplets are extremely rare, but have been observed). The phenomenon of twinning does not alter the importance of the zygote’s producing its own development based on an internal developmental program. Twinning merely indicates that when cells of the early embryo are separated, they retain this internal developmental potency and are able to regenerate the missing cellular components to produce a complete pattern of human development.

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An additional problem with comparing embryogenesis to manufacturing is that, unlike the building of an automobile, there is no actual endpoint to the “building” of a human being. Human development is an *ongoing* process that begins with the zygote and continues seamlessly through embryogenesis, fetogenesis, birth, maturation, and aging, ending only in death. If the zygote is a manufactured “product” of an ongoing developmental process, at what point along this continuum does a human being actually exist? Why is a cell that has undergone syngamy a human zygote and not merely a “unique human cell in the process of becoming a new human, but not there yet”? Indeed, why consider the entity present at the end of embryogenesis or at birth a human being, and not merely “a unique collection of human cells in the process of becoming a new human, but not there yet”? Once a concession has been made to the concept of manufacture and to an arbitrary point at which development has proceeded “far enough” along the assembly line to generate a human being, the precise positioning of this point becomes purely a matter of preference, convenience, and the power to enforce one’s view.

In contrast, if the embryo comes into existence at sperm-egg fusion, a human organism is fully present from the beginning, controlling and directing all of the developmental events that occur throughout life. This view of the embryo is objective, based on the universally accepted scientific method of distinguishing different cell types from each other, and it is consistent with the factual evidence. It is entirely independent of any specific ethical, moral, political, or religious view of human life or of human embryos. Indeed, this definition does not directly address the central ethical questions surrounding the embryo: What *value* ought society to place on human life at the earliest stages of development? Does the human embryo possess the same right to life as do human beings at later developmental stages? A neutral examination of the factual evidence merely establishes the onset of a new human life at a scientifically well defined “moment of conception,” a conclusion that unequivocally indicates that human embryos from the zygote stage forward are indeed living individuals of the human species—human beings.

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AUTHOR

GLOSSARY*

* All definitions are taken from the NIH-administered medical dictionary, (accessed 10/1/08; definitions on file with author; <http://www.nlm.nih.gov/medlineplus/medlineplusdictionary.html>) with minor modifications for clarity, as indicated by italics.

centromere: the point or region on a chromosome to which the spindle attaches during mitosis and meiosis—also called kinetochore.

chromatin: a complex of a nucleic acid with basic proteins (as histone) in eukaryotic cells that is usually dispersed in the interphase nucleus and condensed into chromosomes in mitosis and meiosis.

chromosome: any of the usually linear bodies of the cell nucleus of eukaryotic organisms that take up basophilic stains and contain most or all of the genes of the organism; *a condensed form of chromatin found prior to cell division. When chromosomes have replicated, but are still attached at the centromere, they are called sister chromatids.*

demethylation: the process of removing a methyl group from a chemical compound. *Methyl groups bound to DNA generally inhibit DNA function.*

diploid: having the basic (*haploid*) chromosome number doubled. *Diploid is the normal state for somatic (i.e., body) cells.*

DNA: any of various nucleic acids that are usually the molecular basis of heredity, that are constructed of a double helix held together by hydrogen bonds between purine and pyrimidine bases, which project inward from two chains containing alternate links of deoxyribose and phosphate, and that in eukaryotes are localized chiefly in cell nuclei—also called deoxyribonucleic acid.

embryo: an animal in the early stages of growth and differentiation that is characterized by cleavage, the laying down of fundamental tissues, and the formation of primitive organs and organ systems; especially the developing human individual from the time of *fertilization* to the end of the eighth week after conception (*cleavage commences immediately after fertilization at the two cell stage*).

eukaryote: any of a domain (Eukarya) or a higher taxonomic group (Eukaryota) above the kingdom that includes organisms composed of one or more cells containing visibly evident nuclei and organelles.

fertilization: the process of union of two gametes whereby the somatic chromosome number is restored and the development of a new individual is initiated.

gamete: a mature male or female germ cell (*sperm or egg*) usually possessing a haploid chromosome set and capable of initiating formation of a new diploid individual by fusion with a gamete of the opposite sex—also called sex cell.

gene: a specific sequence of nucleotides in DNA that is located usually on a chromosome and that is the functional unit of inheritance controlling the transmission and expression of one or more traits by specifying the structure of a particular polypeptide and especially a protein or controlling the function of other genetic material—also called determinant, determiner, factor.

genome: one haploid set of chromosomes with the genes they contain.

haploid: having the gametic number of chromosomes or half the number characteristic of somatic cells.

histone: any of various simple water-soluble proteins that are rich in the basic amino acids lysine and arginine and are complexed with DNA.

hydatidiform mole: a mass in the uterus that consists of enlarged edematous degenerated chorionic villi, growing in clusters resembling grapes, that typically develops following fertilization of an enucleate egg, and that may or may not contain fetal tissue.

meiosis: the cellular process that results in the number of chromosomes in gamete-producing cells being reduced to one half and that involves a reduction division in which one of each pair of homologous chromosomes passes to each daughter cell and a mitotic division.

mitosis: a process that takes place in the nucleus of a dividing cell, involves typically a series of steps consisting of prophase, metaphase, anaphase, and telophase, and results in the formation of two new nuclei each having the same number of chromosomes as the parent nucleus.

nucleus: a cellular organelle of eukaryotes that is essential to cell functions (as reproduction and protein synthesis), is composed of nuclear sap and a nucleoprotein-rich network from which chromosomes and nucleoli arise, and is enclosed in a definite membrane.

organism: an individual constituted to carry on the activities of life by means of organs separate in function but mutually dependent: a living being.

ovum (oocyte, egg): a female gamete—especially a mature egg that has undergone reduction, is ready for fertilization, and takes the form of a relatively large inactive gamete providing a comparatively great amount of reserve material and contributing most of the cytoplasm of the zygote.

parthenote: *an individual formed by* development of an unfertilized, usually female, gamete that occurs especially among lower plants and invertebrate animals.

pronucleus: the haploid nucleus of a male or female gamete (as an egg or sperm) up to the time of fusion with that of another gamete in fertilization.

protamine: any of various strongly basic proteins of relatively low molecular weight that are rich in arginine and are found, associated especially with DNA, in place of histone in the sperm of various animals.

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RNA: any of various nucleic acids that contain ribose and uracil as structural components and are associated with the control of cellular chemical activities—called also ribonucleic acid. Messenger RNA is an RNA produced by transcription that carries the code for a particular protein from the nuclear DNA to a ribosome in the cytoplasm and acts as a template for the formation of that protein—also called mRNA.

SCNT/Cloning: *Somatic cell nuclear transfer (SCNT)*; transplanting nuclei from body (*i.e., somatic*) cells to enucleated eggs.

sister chromatid: *see chromosome.*

sperm (spermatozoa): *a sperm cell*; a motile male gamete of an animal usually with rounded or elongate head and a long posterior flagellum.

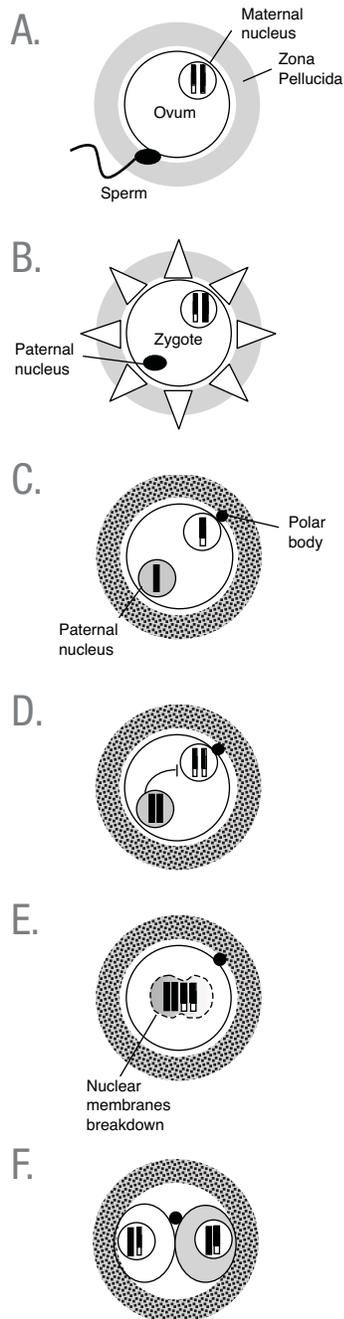
syngamy: sexual reproduction by union of gametes. *Commonly used to refer to the break-down of nuclear membranes of the pronuclei approximately 24 hours after sperm-egg fusion.*

transcription: the process of constructing a messenger RNA molecule using a DNA molecule as a template with resulting transfer of genetic information to the messenger RNA.

translation: the process of forming a protein molecule at a ribosomal site of protein synthesis from information contained in messenger RNA.

zona pellucida: the transparent more or less elastic noncellular glycoprotein outer layer or envelope of a mammalian ovum.

zygote: a cell formed by the union of two gametes; broadly, the developing individual produced from such a cell.



A. Sperm-egg fusion: Prior to fusion, the maternal nucleus is arrested at meiosis II. Sister chromatids (one pair illustrated) are non-identical due to genetic recombination during oogenesis.

B. Zygote formation: The zygote forms immediately upon sperm-egg fusion. Factors from the sperm initiate completion of meiosis II in the maternally derived nucleus. Within 1-3 minutes, changes in cellular calcium initiate the cortical reaction of the zygote, making the cell refractory to fusion with other sperm.

C. Early acts of the zygote: Within 30 minutes, meiosis II is complete, establishing the final diploid genome of the zygote. Sperm binding sites in the zona pellucida are destroyed. Both nuclei undergo decondensation. Paternal DNA is more rapidly and more extensively demethylated than maternal DNA.

D. Onset of zygotic transcription: DNA replication begins at 8-10 hours, converting both nuclei to a (2N) state. Transcription commences immediately following DNA replication. The paternal nucleus suppresses transcription in the maternal nucleus.

E. Syngamy: After approximately 20-25 hours, the pronuclei move together and their nuclear membranes break down. The chromosomes align and mitosis begins immediately.

F. Two-cell embryo: Cell division generates a two-cell embryo. Transcription increases and development beyond this stage depends on zygotic transcription. Evidence suggests that each cell is biased towards distinct developmental paths, and that they interact coordinately to orchestrate subsequent development.

FIGURE 1

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