What Is an Embryo?

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> *About twenty seven years ago I began to think of attempting the compilation of a Dictionary. I was induced to this undertaking . . . by my own experience of the want of such a work, while reading modern books of science . . . . [T]he nature of our governments, and of our civil institutions, requires an appropriate language in the definition of words . . . .*[1]

I. INTRODUCTION AND DEFINITION OF THE PROBLEM

Most scientific and medical discoveries are accompanied by new terms to describe the new processes. Although this imposes the burden on society of continually learning a new lexicon, new terminology clarifies that the societal impact of emerging technologies needs to be newly interpreted.

A notable exception to this general practice, however, has been the failure to develop new terms to describe the new demands placed on mammalian eggs. Approximately 250 times the size of a somatic cell,[2] and 4,000 times the size of a sperm head, the mammalian egg is a highly specialized cell which has stockpiled a collection of enzymes and other molecules that empower it to completely remodel the chromosomes[3]

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[1] NOAH WEBSTER, AN AMERICAN DICTIONARY OF THE ENGLISH LANGUAGE, at Preface (1828).

[2] All the cells in the body except for sperm and eggs and their precursor cells, which are collectively termed "germ cells."

[3] Human genetic information is divided into twenty-three chromosomes which are polymers of deoxyribonucleic acids that comprise genes arranged end to end. At the time cells divide, individual chromosomes are tightly coiled and can be distinguished from each other; at all other times, they are

brought in by sperm, and then to carry out a series of faithful duplications of both the sperm chromosomes and its own. The biologic goal is clear—to generate new and exact copies of the paternal and maternal genes as quickly as possible and apportion them equally within new daughter cells.

Details of the powerful sperm remodeling capability of eggs are poorly understood, particularly with respect to human eggs. Because of the global population explosion, and a view by some that life begins at fertilization, more research funds are allocated to preventing fertilization than to understanding the details of the process. This is especially true in the United States, which has a congressional moratorium to prevent the use of federal dollars to study fertilized human eggs.[4]

The advent of microscope tools to manipulate individual eggs and smaller cells provided the opportunity for reproductive biologists to begin to probe the power of the mammalian egg to remodel chromosomes from a variety of cells, not just sperm heads. The questions in need of answers had intrigued scientists for many years.

Does the process of becoming a mature, functioning member of a specific organ, such as the liver, permanently alter the chromosomes within the cell? The term for the process is "differentiation." For example, during fetal development, some cells differentiate into liver cells and it is critically important to the health of the fetus, as well as the offspring after birth, that the new liver cells carry out the normal functions of the liver and not randomly change into other types of cells. A fundamental question, therefore, is does the process of differentiation irreversibly alter the chromosomes in the cell so that they no longer have the capacity to become another type of cell? Has the genetic information in the chromosomes of the liver cell been permanently modified, amplified, or removed so that only liver-conferring genetic information remains? Or do mature liver cells contain the same complement of genes as embryonic cells with some being silenced and others actively expressed? If the latter is the case, can the mature liver cell's genes be "re-programmed" or "de-differentiated" into the same format as embryonic genes?

Another fundamental question relates to the interaction between the egg and sperm, whose chromosomes contain proteins peculiar to sperm heads. Can eggs only remodel certain types of chromosomes such as those in sperm heads? Or can eggs remodel chromosomes from a variety of cell types? Once the microscope tools were available, the obvious experiment to address both questions was to transplant chromosomes from a fully differentiated cell into an egg. Since chromosomes are contained within

loosely coiled, allowing their genes to be more spread apart. There are two copies of each chromosome in somatic cells, one from the father via the sperm and one from the mother via the egg. Mature sperm contain one copy. Mature eggs contain two copies until fertilization takes place, at which time one copy of each chromosome is extruded from the egg cytoplasm.

[4] Balanced Budget Downpayment Act, Pub. L. No 104-99, § 128, 110 Stat. 26, 34 (1996).

the nucleus of a cell, the term for this technology is "nuclear transplantation."

Work to date has proven that eggs can remodel chromosomes other than the sperm's and that the nuclei of at least some types of cells[5] can be fully de-differentiated. The ultimate scientific test of the functional capacity of the genes contained within the transplanted, remodeled nucleus is whether or not they can direct the formation of a new offspring. These types of experiments developed the technology that eventually led to cloning Dolly the sheep,[6] and Amy the cow.[7]

Historically, the goal of this line of research was not to clone valuable animals, but to answer questions about the fundamental biology. Throughout the many decades of this research, biologists used a variety of terms to describe the stages of activated eggs, including "cleaving eggs," "ova," "zygote," and "embryo." As reproductive biologists, they were fully aware that the vast majority of "embryos," however created, do not have the capacity to give rise to offspring. They, therefore, did not feel the need to develop new terms to distinguish "embryos" created by laboratory manipulations from embryos created by fertilization by sperm.

But the powerful promise of stem cell technology to alleviate currently untreatable diseases has brought about rancorous social and political debates which have revealed widespread confusion. That the debates have occurred bespeaks a healthy society with concern for the well being of the least of its members. Nonetheless, the evident confusion reveals a compelling need to describe and define the biological processes with greater clarity. Within that framework, there is value in considering the historic, scientific, and legal definitions of "embryo." Legislators and courts looking to biologists for clear definitions have discovered an uncharacteristic lack of scientific rigor in the terminology available.

The advent of assisted reproductive technologies for infertile humans afforded the opportunity to directly observe laboratory dishes containing elegant human eggs with their surrounding vestments of helper cells and frantically moving human sperm. The profound intimacy and strict

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[5] To date, offspring have been obtained following transplantation of nuclei from skin cells (commonly used to clone cattle), cells in the ovary surrounding the egg, and cells from the testis, uterus, mammary gland, and muscle. Lesley Paterson, *Somatic Cell Nuclear Transfer (Cloning) Efficiency* (2001), *available at* http://www.reproductiveclong.net/hosting/waite/efficiency.pdf (last visited Mar. 4, 2004) (on file with the Connecticut Law Review).

[6] I. Wilmut et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, 385 NATURE 810, 810-11 (1997).

[7] Chikara Kubota et al., *Six Cloned Calves Produced from Adult Fibroblast Cells After Long-Term Culture*, 97 PROC. OF THE NAT'L ACAD. OF SCI. OF THE U.S. 990, 990-995 (2000), *available at* http://www.geocities.com/uconnyanglab/yang.pdf (last visited Apr. 17, 2004) (on file with the Connecticut Law Review); *Bovine Telomere Length Reprogrammed News Release*, June 10, 1999, *available at* http://www.geocities.com/uconnyanglab/amy.html (last visited Mar. 5, 2004) (on file with the Connecticut Law Review) [hereinafter *Bovine Telomere*].

orchestration required to bring together these two highly specialized cells from two unique individuals in order to continue the species in the form of a new human being demands the utmost respect and sanctity. Words used to describe this unique process should be as special and specific as the process itself.

This Article is undertaken not with the goal of disputing or refuting any existing viewpoints of human reproduction, or when life begins, but rather to make room in those viewpoints for the emerging technologies which appear at the outset to threaten the sanctity of the union of sperm and egg. Some of these issues have been considered previously, first in the context of human fetal research in the early-1970s,[8] again in the late-1970s and in 1993 in the context of assisted reproductive technologies,[9] and again in 1999 and 2001 in the context of embryonic stem cell research.[10] Review of the reports from those discussions reveals confusing use, and misuse, of some terms. The present goal is to present compelling arguments that although the new technologies result in entities morphologically similar to early human entities, and may have some potential for development to an offspring, terms specific for each technology are essential for the clarity needed to make fully informed policy decisions and establish appropriate guidelines and laws. Most members of society are not reproductive biologists familiar with the wondrous capabilities, and frailties, of human eggs.

II. THE BIOLOGY OF REPRODUCTION

All eggs, sperm, and embryos are not created equal. It is a basic tenet of biology.

A. *Sperm and Eggs*

Frogs elaborate billions and billions of sperm and eggs into the pond

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[8] DEP'T OF HEALTH, EDUC., AND WELFARE, BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979), *available at* http://history.nih.gov/history/laws/belmont.html (last visited Apr. 16, 2004) (on file with the Connecticut Law Review) [hereinafter BELMONT REPORT].

[9] UC TASK FORCE ON PRACTICE STANDARDS FOR ASSISTED REPROD. TECH., UNIV. OF CAL. ASSISTED REPRODUCTIVE TECHNOLOGY: A SYSTEMWIDE TASK FORCE REPORT AND RECOMMENDATIONS TO STRENGTHEN OVERSIGHT AND IMPROVE QUALITY OF CARE 11-13 (1996), *available at* http://www.ucop.edu/healthaffairs/reports/welcome.html (last visited Mar. 7, 2004) (on file with the Connecticut Law Review). *See also* AMER. SOC'Y REPROD. MED., AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE ETHICS REPORTS, *in* 62 FERTILITY & STERILITY ch. 26 (Supp. I 1994).

[10] NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH 85 (1999), *available at* http://www.georgetown.edu/research/nrcbl/nbac/stemcell.pdf (last visited Apr. 16, 2004) (on file with the Connecticut Law Review) [hereinafter ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH]; Gene Outka, *The Ethics of Stem Cell Research* (2002), *available at* http://bioethics.gov/background/outkapaper.html (last visited Mar. 7, 2004) (on file with the Connecticut Law Review).

each spring—in the hope that a tiny percentage will fertilize, develop into embryos, then into tadpoles and then into frogs. The same is true for pea seedlings—many germinate, only a few survive to produce a new generation of peas. All of nature comprehends that the path to a mature, reproductive adult is fraught with biological failure, even in the absence of predators or environmental toxins. This risk to survival of the species is generally met with sheer numbers of organisms initiated.

Not so with mammals. Although billions of sperm are produced daily by some mammalian males, female mammals are far more conservative. They produce a few eggs, at defined intervals, and rely on their ability to nurture and protect the precious few offspring that ensue until the offspring themselves reach the age of reproductive competence. Hence, the rate-limiting step in survival of mammals is the fitness of the mammalian egg.

Humans are no exception. Following puberty, most men produce more sperm than hair follicles each day of their lives; estimates range from fifty to five hundred million sperm per day. In contrast, women are born with on the order of one million immature eggs in their ovaries. By the time they are fifty-five years old, the eggs are all gone, although only approximately five hundred were matured and released during their four decades of monthly ovulatory cycles.[11] Hence, in the human, billions and billions of sperm chase a dozen or so eggs each year to ensure survival of the species.

Eggs and sperm are collectively referred to as "gametes." They contain all the genetic information inherited from parents. The life cycle of gametes includes unusual rearrangements of the chromosomes, termed "crossing-over," that recombines each chromosome so that some of the genes come from the father and some from the mother. In addition, immature gametes actually contain four copies, not two, of each chromosome during the "crossing-over" stage. Once the chromosomal rearrangements have taken place, the gametes are ready to undergo final maturation.

Four individual, motile sperm develop from each immature spermatozoan. Each sperm head contains one copy[12] of each newly rearranged chromosome, not two copies as in somatic cells. Since chromosomal "crossing-over" appears to be relatively random, each sperm head contains twenty-three chromosomes with a unique mixture of

[11] The process of releasing an egg each month is termed ovulation. The vast majority of eggs in the human ovary are in a quiescent state waiting to be recruited to enter the final stages of maturation that will lead to ovulation. One or a few eggs are stimulated each month by hormones from the pituitary gland. The process by which an individual egg is selected is not known with certainty. It takes approximately two weeks to ready the selected egg for release from the ovary into the fallopian tube wherein it may encounter sperm. The fallopian tube connects the ovary with the uterus.

[12] One copy of each chromosome is termed haploid; two copies of each chromosome is termed diploid, the normal state for a somatic cell.

maternal and paternal genes. Half the sperm contain an X chromosome, and the other half contain a Y chromosome.

In contrast, immature eggs do not mature to a haploid state. Instead of developing four eggs, each with a haploid set of chromosomes, eggs maintain four copies of all twenty-three chromosomes until just before ovulation. At ovulation, half the chromosomes are extruded from the egg in the form of a much smaller cell termed a "polar body." These chromosomes will eventually degenerate and are not thought to play a role in embryonic development. At this stage, the egg is diploid and arrested in development, awaiting fertilization.

The majority of human eggs, on the order of 20,000 per year, die in the ovary by mechanisms that are not understood. The phenomenon is termed "atresia." Only a dozen or so are ovulated each year during the monthly menstrual cycle. Following puberty, therefore, the monthly ovulatory cycle of women recruits eggs from a reservoir that has an increasing percentage of dying members. Which eggs get recruited, whether or not they are robust or dying, and how to measure their potential for full development to offspring is not known with certainty.

Sexual reproduction is naturally fraught with pitfalls. The magnitude of the task of a single egg to engender a new individual is, of itself, the reason it fails far more often than it succeeds. Failure can occur at many stages.

Each member of mankind begins with a single cell, the union of sperm and egg, each with a set of half the necessary chromosomes needed to give rise to a new individual. The majority of such unions fail to develop, however, due to inherent defects in either the sperm or the egg. Such defects are a natural feature of the biology of sperm and egg formation. Given that reproduction is the most important function of a species, preservation of maternal resources must be a central element of reproduction. The existence of checkpoints to test the viability of each union of sperm and egg seems intuitively obvious in order to preserve maternal resources. Such is the case. As described in the sections to follow, reproduction in man includes the need for the prospective conceptus[13] to express specific gene products throughout development to ensure its own survival. Failure to signal the mother that development is progressing within normal limits results in spontaneous maternal reversion to a non-pregnant state with expulsion of the failed conceptus. Such mechanisms to ensure the robustness of offspring are probably as important to survival of the species as the capacity for reproduction itself. Nature

[13] "Conceptus" is a general term used to describe all stages of embryo and fetal development, including fetal membranes and placenta.

celebrates success and disdains failure.

B. *Fertilization*

The egg may fail to fertilize, a complex process with many steps. Sperm may be unable to penetrate the egg coatings.[14] Sperm that do penetrate may then fail to be remodeled. Hence, development can go no further. Within a few days, the egg will die, just as if it had never been penetrated by a sperm. Several lines of evidence suggest that some eggs undergoing atresia may be selected for release into the fallopian tube and uterus that month.[15] Their capacity to carry out normal egg functions is limited. Failure to remodel the sperm head may, therefore, be due to either problems within the egg or within the sperm itself. Such an egg has been penetrated, but it is not fertilized, because there has been little or no actual interaction between the sperm and the egg. In a day or so, the egg and sperm will naturally disintegrate. Such an early failure of union of sperm and egg will go unnoticed by the mother.

Figure 1[16]

Under more successful circumstances, immediately after sperm penetration the egg must eliminate half of its remaining forty-six chromosomes to match the twenty-three chromosomes brought in by the sperm. The extra twenty-three chromosomes are split off from the egg in the form of a second polar body. This step could fail either completely or partially, leaving behind too many or too few egg chromosomes, a state

[14] The egg is a huge cell surrounded by a specialized carbohydrate and protein coat termed the "zona pellucida," because of its clear appearance, which is in turn surrounded by millions of granulosa cells from the ovary which provide nutrients to the egg throughout its development by way of projections that extend through the zona pellucida.

[15] P. Hyttel et al., *Ultrastructure of Human Cumulus-Oocyte Complexes from Healthy and Atretic Follicles*, 1 HUM. REPROD. 153, 153 (1986).

[16] ANN A. KIESSLING & SCOTT C. ANDERSON, HUMAN EMBRYONIC STEM CELLS: AN INTRODUCTION TO THE SCIENCE AND THERAPEUTIC POTENTIAL, (2003), reprinted with permission from Jones and Bartlett Publishers, Sudbury, MA, www.jbpub.com.

generally incompatible with life.[17] In theory, the accuracy of the chromosomal division could be determined by analysis of the chromosomes contained within the second polar body.

If the sperm head undergoes remodeling, the process is initiated immediately by factors within the egg. Within a few hours, the result is an unusually large nucleus, termed a "pronucleus." A second, large pronucleus forms around the remaining twenty-three egg chromosomes. The appearance of two pronuclei defines a "zygote."[18] (Figure 1) Within the pronuclei, faithful duplication of each chromosome is immediately initiated to produce one complete copy of the chromosomes brought in by the egg and those brought in by the sperm. This duplication process is fraught with pitfalls.

Figure 2[19]

First, either the sperm chromosomes or the egg chromosomes could be flawed. Such flaws are relatively common in cells. Second, most cells that undertake the task of chromosome duplication have not practiced recently. Eggs, especially human eggs, have not duplicated chromosomes since the ovary was formed during the woman's fetal development—on the order of a decade and a half, and up to four decades. Faithful copying of each chromosome is absolutely essential to successful development of a normal, healthy offspring. Sperm heads do not contain the enzyme machinery needed to copy the sperm chromosomes. That machinery resides within the egg, but there is very little scientific evidence about the nature of this reservoir of enzyme machinery. In most cells that divide regularly, the enzymes are synthesized when needed and degraded when the task is

[17] One exception to this is three copies of chromosome 21, trisomy 21 (Down's syndrome).

[18] From the Greek word, *zygous*, meaning yoked.

[19] KIESSLING & ANDERSON, *supra* note 16. Reprinted with permission from Jones and Bartlett Publishers, Sudbury, MA, www.jbpub.com.

completed. This cannot be the case with eggs because DNA replication begins immediately upon formation of the pronuclei and the process does not require the synthesis of new proteins. If the machinery, which has been dormant for many years, has even a tiny flaw, the process itself could be imperfect. Flawed duplication of genes within the chromosomes at this initial stage could result in defective genes within all the new cells subsequently produced.

Gene defects put in place during the first cycle of chromosome duplication may not be apparent until their protein products are needed for the next stage of development. For example, at the stage when the embryonic heart muscle must begin to contract to pump the nutrients needed for continued development, genetic defects in heart muscle proteins created many days before, during the early stages of fertilization, will bring about demise of the embryo.[20] It will be expelled from the uterus and the mother will return to a non-pregnant state, in preparation for a new attempt at conception.

At the end of the DNA replication in both the male and female pronuclei, perhaps even if it has been flawed, the two pronuclei migrate together to the middle of the egg. Chromosome formation begins, the pronuclear membranes dissolve, and the maternal and paternal chromosomes line up—hopefully in a fashion that will allow one of each to become apportioned into the new daughter cells. The cellular machinery that then drives separation of chromosomes into two new cells is activated, and the first cleavage division occurs. (Figure 2) The result: two new cells with half the volume of the original egg. Defects in the cellular machinery required to carry out division of the egg into two cells can result in developmental arrest and eventual expulsion from the mother.

Does the formation of two-cells define the completion of fertilization? This is an important question for those who believe that life begins at fertilization. In fact, it is difficult to define the beginning, and the end, of fertilization. Sperm penetration of the egg is a minimal requirement for the beginning, and cleavage to two cells with both male and female chromosomes in each nucleus may mark the end, but there are several caveats. One is that the egg can cleave to two cells without being

[20] Yang Luo et al., *Rescuing the N-Cadherin Knockout by Cardiac-Specific Expression of N- or E-Cadherin*, 128 DEVELOPMENT 459, 459 (2001). This circumstance is somewhat ameliorated by the fact that there are at least two copies of most genes, one from the sperm and one from the egg. It is important to note that errors created in the first DNA replication will affect at least twenty-five percent of all cells for life. In the male, moreover, there is only one copy of the X chromosome and one copy of the Y chromosome, rendering the gene products in those two chromosomes especially vulnerable to mutations. Hemophilia is an example of a gene defect in an X chromosome: males with only one X chromosome manifest the disease; women, with two X chromosomes, generally do not manifest the disease because it is exceedingly rare to have mutations in both chromosomes simultaneously.

penetrated by sperm, as will be discussed in a later section. Secondly, strong arguments can be made that fertilization is complete only when the sperm's genes are first activated. Evidence suggests this is coincident in time with observed pauses in development. Without sperm gene activation, the sperm's contribution to the process is limited to the egg activating enzymes elaborated at the time of penetration. Whether or not an egg is truly fertilized if the sperm genes never participate is a matter for debate.

C. *Cleavage*

The early cell cycles are termed "cleavages" because each daughter cell is half the size of the cell before it; the cells themselves are termed "blastomeres" to designate their uniquely large size and their potential to give rise to all cells in the body. The next cell cycle, which will generate two new daughter cells from each of the two-cells, giving rise to four-cells, also requires faithful duplication of the two-cell chromosomes. Several lines of evidence suggest that the enzyme machinery required for the second and third rounds of chromosome duplication is also left over from the egg.[21] Each cell undergoing duplication has an independent risk of being flawed. Hence, one two-cell blastomere could carry out accurate gene duplication and the other one not, giving rise to a four-cell with two having "normal" sets of chromosomes and two "abnormal." As stated earlier, flaws in duplication of the genes within each chromosome may or may not be apparent until later stages of development.

The process of gene duplication and cell cleavage repeats itself over and over. The resulting daughter blastomeres remain intimately associated with each other because of the boundary provided by the zona pellucida which originally surrounded the egg. At some point, unknown at this time for humans, the blastomeres exhaust the egg supplies of the enzyme machinery responsible for duplicating the chromosomes and must synthesize new components. At approximately the thirty-two- to sixty-four-cell stage, four to five days after sperm entry, the blastomeres have reduced in size to the equivalent of somatic cells. At this point, the cells must each grow a little before cell division occurs to allow for the production of two daughter cells. By this time, proteins are synthesized from both maternal and paternal genes in order to bring about continued development. Fertilization is clearly completed by this stage.

D. *Morula*

The transition from four-cells to eight-cells heralds the morula stage.

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[21] *See* Ann A. Kiessling et al., *Development and DNA Polymerase Activities in Cultured Preimplantation Mouse Embryos: Comparison with Embryos Developed In Vivo,* 258 J. EXPERIMENTAL ZOOLOGY 34, 34 (1991).

At approximately the twelve to fourteen cell-stage, the geometry of the ball of blastomeres captures one or two inside their cluster.[22] Generally thought to be a random event, recent evidence suggests the inside cells may be selected for this position earlier in development.[23] This marks the first developmental stage in which some cells touch only other cells instead of being exposed to the environment. This event heralds the commitment of the inside cells to developing into the embryo and the outside cells to giving rise to the placenta. This stage may be reached whether or not some, or all, of the cells contain flawed genetic information.

E. *Blastocyst*

The outside cells form tight junctions with each other, creating a sealed barrier against the environment. They begin to pump water and nutrients toward the interior of the cell cluster, giving rise to an internal cavity.[24] At one end of the cavity, the inner cells aggregate and continue to divide into new daughter cells forming a mass termed the "inner cell mass" ("ICM"). Failure to form a robust ICM leads to blunted embryonic development and a high probability of failure.

F. *Implantation*

Development to a blastocyst takes on the order of five to eight days for mammals and proceeds as the embryo journeys through the fallopian tube and into the uterus. Once in the uterus, it will undergo implantation,[25] followed by a period of rapid growth characterized by the formation of the embryonic disc,[26] on the dorsal side of which the primitive streak will form. The primitive streak defines the embryo with respect to head, tail, back, and belly.[27] Shortly thereafter, three layers of cells can be distinguished in the embryonic disk and organogenesis begins.[28] Once all

[22] Beyond the four-cell stage of development, the cleaving blastomeres resemble a blackberry, a stage termed the "morula" stage of development.

[23] Maria Anna Ciemerych et al., *Animal and Vegetal Poles of the Mouse Egg Predict the Polarity of the Embryonic Axis, Yet are Nonessential for Development*, 127 DEVELOPMENT 3467, 3467 (2000).

[24] The fluid-filled cavity is termed the "blastocoel."

[25] "Implantation" is the interaction between the blastocyst and the lining of the uterus that leads to the formation of the placenta.

[26] The ICM is bounded on one side by the blastocoel and on the upper side by the developing fluid-filled amniotic cavity. The result is a pancake-like bilayer of cells termed the "embryonic disc," comprised of primitive endoderm on the blastocoel side and embryonic ectoderm on the amniotic cavity side. ANN A. KIESSLING & SCOTT C. ANDERSON, HUMAN EMBRYONIC STEM CELLS: AN INTRODUCTION TO THE SCIENCE AND THERAPEUTIC POTENTIAL 98-99 (2003).

[27] *Id.* at 111-13.

[28] Three distinct layers of cells form in the embryonic disk: endoderm, mesoderm, and ectoderm, which are termed "embryonic germ layers." *See id.* at 112-14.

rudimentary organs are in place, the developing offspring is termed a "fetus."

The precision with which the early events in an activated egg must be accomplished highlight the potential for reproductive failure, which appears to be an inherent biologic phenomenon. Several lines of evidence suggest approximately one in three or four fertilized eggs from young women will give rise to a baby, whereas one in ten or twenty fertilized eggs from an older woman will be successful.[29] This potential for embryologic failure may have given rise to the profound human interest in repeated attempts.

It is important to highlight some of nature's checks and balances with respect to human embryonic and fetal development. First is the absolute requirement that the conceptus send a signal to the mother that it is developing. Human chorionic gonadotropin is a hormone synthesized as early as the morula stage,[30] which reaches detectable levels in the mother's blood by the time the blastocyst begins the process of implantation. In the absence of this signal, the uterus initiates a menstrual period and the ovary prepares to mature another egg or two for the following month's attempt to achieve a pregnancy. Thus, nature has no regard for an early conceptus that cannot announce its presence to the mother in a timely fashion. It will simply be expelled in preparation for another attempt. In fact, production of this hormone must continue to double every few days even after implantation in order to signal a growth rate that the uterus and ovary recognize as within normal limits. If the implanted blastocyst fails to do this, the pregnancy will fail and the blastocyst will be expelled with the menstrual flow. "Blighted ovum" is the term applied to pregnancies that fail within the first few weeks of development.

Second is the requirement that each fetal organ must begin to function normally at the time it is needed for continued development. These are rigorous developmental milestones clearly designed to bring to birth only those fetuses that are developing within normal limits. Given the intense nurturing required by mammalian young, the developmental rigor imposed before birth seems designed to conserve maternal resources. Failed development promptly leads to abortion, thus opening the way for another attempt.

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[29] Griffith Feeney, *Fertility Decline in East Asia*, 266 SCIENCE 1518, 1519-1520 (1994); Charles F. Westoff, *Fertility in the United States*, 234 SCIENCE 554, 556-57 (1986). *See also* NAT'L CTR. FOR HEALTH STAT., NATIONAL VITAL STATISTICS—NATALITY, *available at* http://www.cdc.gov/nchs/births.htm. (last visited Apr. 16, 2004) (on file with the Connecticut Law Review).

[30] *See generally* Alexander Lopata & David L. Hay, *The Surplus Human Embryo: Its Potential for Growth, Blastulation, Hatching, and Human Chorionic Gonadotropin Production in Culture*, 51 FERTILITY & STERILITY 984 (1989).

G. *Totipotent and Pluripotent Cells*

The work of many scientists has concluded that at least until the eight-cell stage, each blastomere has the potential to contribute to all fetal tissues, including those of the offspring and the placenta.[31] These cells are therefore described as "totipotent." Once the blastocyst forms, the outer, trophoblast cells have restricted their developmental potential to formation of the placenta and embryonic membranes, whereas the ICM cells maintain the capacity to contribute to all the tissues of the fetus, with a reduced capacity to contribute to the placenta. For this reason, ICM cells are termed "pluripotent," which explains the pluripotency of embryonic stem cells.

It is important to recognize that an inability to develop to a healthy offspring does not, however, necessarily negate the potential of the fertilized egg to give rise to stem cells. Thus, it is possible that many eggs traditionally doomed to die during embryogenesis could be utilized for stem cell production. Mouse embryos doomed to die in the reproductive tract survive to the blastocyst stage in laboratory culture.[32] This notion highlights the urgent need to be able to distinguish developmentally capable fertilized eggs from incapable fertilized eggs.

H. *Summary*

Human reproduction is as fraught with natural biological failure as other mammalian reproduction. In fact, human reproduction may be more failure prone than other mammals because female humans delay fertilization of their eggs until at least the second, and more commonly the third or fourth, decade of life. Fertilization may begin with sperm entry into the egg, but the process is fraught with failure, and the completion of fertilization is not known with precision. "Zygote" is a term that applies specifically to the union of sperm and egg. Historically, it is a term used by embryology texts, medical, and law dictionaries to refer to the appearance of two pronuclei, followed by the first two to three weeks of development of the fertilized egg. That time frame encompasses the developmental stage that is primarily the responsibility of the egg, recognizing that the contribution of sperm genes appears toward the end of

[31] H.T. Cheong et al., *Birth of Mice After Transportation of Early Cell-Cycle-Stage Embryonic Nuclei into Enucleated Oocytes*, 48 BIOLOGY OF REPROD. 958 (1993), *available at* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=npg&cmd=Retrieve&db=PubMed&list_uids=8481482&dopt=abstract (last visited Mar. 3, 2004) (on file with the Connecticut Law Review). *See also* S.J. Kelly, *Studies of the Developmental Potential of 4- and 8-Cell Mouse Blastomeres*, 200 J. EXPERIMENTAL ZOOLOGY 365 (1977); Beatrice Mintz, *Formation of Genetically Mosaic Mouse Embryos and Early Development of Lethal (t12/t12)-Normal Mosaics*, 157 J. EXPERIMENTAL ZOOLOGY 272 (1964); Andrezj K. Tarkowski et al., *How Many Blastomeres of the 4-Cell Embryo Contribute Cells to the Mouse Body?*, 45 INT'L J. DEVELOPMENTAL BIOLOGY 811 (2001).

[32] Kiessling et al., *supra* note 21, at 45-46.

this period. It is the responsibility of the conceptus to signal the uterus that it is developing normally so the uterus will maintain the pregnancy.

III. HISTORICAL DEFINITIONS OF "EMBRYO"

No other word involved in the debates about harnessing the power of the human egg to remodel chromosomes calls up such an emotional response as "embryo." It embodies the very essence of that which requires protection and nurturing. An embryo is the least of ourselves. The notion is of a struggling new being that will gain independence if simply allowed to progress unimpeded and with appropriate support from society.

As covered in the previous section, nature does not hold the embryo in such a lofty position. Human reproduction is engineered to eliminate support for defective embryos as quickly as possible in order to allow a repeat attempt. Survival of the fittest is nature's prevailing paradigm for embryos.

Given that society's view is vastly more generous than nature's view, the task before us is to come to a new view of the concept of "embryo."[33]

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[33] To begin to develop a new view of what an "embryo" is, it is helpful to survey society's past and present positions.

A. Lay Public Dictionaries

An American Dictionary of the English Language defines "embryo," as: "[T]he first rudiments of an animal in the womb, before the several members are distinctly formed; after which it is called a fetus. 2. The rudiments of a plant. 3. The beginning or first state of any thing not fit for production; the rudiments of anything yet imperfectly formed." AN AMERICAN DICTIONARY OF THE ENGLISH LANGUAGE (1828). "Zygote" is not listed. *Webster's New World Dictionary of the American Language, Concise Edition* defines "embryo" as: "1. an animal in the earliest stages of its development in the uterus: the human organism in the first three months after conception is called an *embryo*, thereafter a *fetus*. 2. *a*) an early, undeveloped stage of something. *b*) anything in such a stage. 3. in *botany*, the rudimentary plant contained in the seed." WEBSTER'S NEW WORLD DICTIONARY OF THE AMERICAN LANGUAGE, CONCISE EDITION 245 (1956). "Zygote," is defined as "any cell formed by the union of two gametes." *Id.* at 882. In 1990, *Webster's New World Dictionary* defined "embryo" as: "1. an animal in the earliest stages of its development in the uterus[.] 2. the rudimentary plant contained in a seed[.] 3. an early stage of something[.]" WEBSTER'S NEW WORLD DICTIONARY 195 (1990). "Zygote" is defined as: "[A] cell formed by the union of male and female gametes." *Id*. at 689.

B. Medical Dictionaries

In 1959, *Taber's Cyclopedic Medical Dictionary* defined "embryo" as: "1. The young of any organism in an early stage of development. 2. Stage in prenatal development of a mammal between the ovum and the fetus. In humans, stage of development between the second and eight weeks, inclusive," and "embryo, development of" as:

> 1. *Period of the ovum*; (first two weeks) Blastocyst forms, enters uterus and implantation occurs. 2. *Period of the embryo* (3rd to 8th weeks). Embryo increases in length from about 1.5 mm to 23mm. Organ systems arise and embryo acquires human form. 3. *Period of the fetus* (3rd to 9th month).

TABER'S CYCLOPEDIC MEDICAL DICTIONARY E-16 (8th ed. 1959).

In 1981, *Taber's Cyclopedic Medical Dictionary* defined "embryo" as: "1. The young of any organism in an early stage of development; 2. Stage in prenatal development of mammal between the ovum and the fetus; in humans, stage of development between the 2nd and 8th weeks, inclusive," and:

> Develop: *Zygote*: (1st week); Following fertilization, cells multiply (cleavage) which results in formation of a morula, which in turn develops into a blastocyst consisting of a trophoblast and inner cell mass. Two cavities (amniotic cavity and yolk sac) arise within the inner cell mass. These are separated by the embryonic disk which gives rise to three germ layers (ectoderm, mesoderm, and endoderm), these developing into the embryo proper. The blastocyst wall of trophoblast gives rise to auxiliary structures. The zygote enters the uterus and implantation occurs; *Embryo* (2nd through 8th weeks); The embryo increases in length from about 1.5 mm to 23 mm. The germ layers of the embryonic disk give rise to the principal organ systems and the embryo begins to show the human form; *Fetus* (3rd to 9th months).

TABER'S CYCLOPEDIC MEDICAL DICTIONARY Z-4 (14th ed. 1981).

In 2001, *Taber's Cyclopedic Medical Dictionary* defined "embryo" as:

> 1. The young of any organism in an early stage of development. 2. In mammals, the stage of prenatal development between fertilized ovum and fetus. In humans, this stage begins on day 15 after conception and continues through gestational week 8; Development: During this early stage of tissue differentiation and organogenesis, the human embryo is most vulnerable to damage from maternal viral infections such as rubella and from toxic chemicals such as alcohol and tobacco smoke. *Zygote* (First week): Following fertilization, cells multiply (cleavage), resulting in the formation of a morula, which in turn develops into a blastocyst consisting of a trophoblast and inner cell mass. The trophoblast gives rise to the fetal membranes and placenta after the blastocyst enters the uterus and begins implantation. *Zygote* (Second week); Two cavities (amniotic cavity and yolk sac) arise within the inner cell mass. These are separated by the embryonic disk, which in the second week consists of an ectoderm and an endoderm layer. *Zygote* (Third week): A mesoderm layer forms between the ectoderm and endoderm layers, and these three germ layers develop into the embryo proper. *Embryo* (Second through eighth weeks): The embryo increases in length from about 1.5 mm to 23 mm. The germ layers of the embryonic disk give rise to the principal organ systems, and the embryo begins to show human form. During this period of organogenesis, the embryo is particularly sensitive to the effects of viral infections of the mother (e.g. rubella) and toxic chemicals, including alcohol and tobacco smoke, and is sensitive to hypoxemia.

TABER'S CYCLOPEDIC MEDICAL DICTIONARY 683 (19th ed. 2001); while defining "pre-embryo" as: "The morula and blastocyst stages produced by the division of the zygote until the formation of the embryo proper at the appearance of the primitive streak about 14 days after fertilization." *Id*. at 1729-30; additionally, *Stedman's Practical Medical Dictionary* in 1939 defined "embryo" as:

> 1. A rudiment. 2. The rudimentary plant in the seed. 3. The product of conception during its intrauterine existence; its first two weeks constitute the ovum stage; from the end of the 2d to the beginning of the 8th week is the embryonal stage, and from the beginning of the 3d month to the termination of gestation is the fetal stage.

STEDMAN'S PRACTICAL MEDICAL DICTIONARY 384 (14th ed. 1939).

In 1961, *Stedman's Medical Dictionary* defined "embryo" as: "1. An organism in the initial stages of its development. An individual from the fertilization of the ovum to birth or to its emergence from the egg. In man the embryonic stage beyond the 3rd month of gestation are frequently designated as fetal. 2. A rudimentary plant within a seed." STEDMAN'S MEDICAL DICTIONARY 509 (20th ed. 1961).

In 1972, the twenty-second edition defined "embryo" as: "1. An organism in the early stages of development; in man, from conception until approximately the end of the second month. Developmental stages from this time to birth are commonly designated as fetal. 2. A primordial plant within a seed." STEDMAN'S MEDICAL DICTIONARY 404 (22d ed. 1972).

In the twenty-sixth edition of *Stedman's Medical Dictionary*, "embryo" is defined as: "1. An organism in the early stages of development. 2. In humans, the developing organism from conception until approximately the end of the second month; developmental stages from this time to birth are commonly designated as fetal. 3. A primordial plant within a seed," "conception" is defined as "1. SYN concept. 2. Act of forming a general idea or notion. 3. Act of conceiving, or becoming pregnant; fertilization of the oocyte (ovum) by a spermatozoon to form a viable zygote," and "conceptus" is

defined as "the product of conception, *i.e.* embryo and membranes." STEDMAN'S MEDICAL DICTIONARY 559, 377 (26th ed. 1995).

In 2000, *Stedman's Medical Dictionary* defined "embryo" as: "1. An organism in the early stages of development. 2. In humans, the developing organism from conception until approximately the end of the second month; developmental stages from this time to birth are commonly designated as fetal. 3. A primordial plant within a seed," while "pre-embryo" was not listed. STEDMAN'S MEDICAL DICTIONARY 601 (27th ed. 2000).

C. Human Embryology Textbooks

Figure 2-8 in *Langman's Medical Embryology* is a depiction of the:

> Schematic representation of the development of the zygote from the two-cell stage to the late morula stage. The two-cell stage is reached approximately 30 hours after fertilization; the four-cell stage at approximately 40 hours; the 12- to 16-cell stage at approximately three days; and the late morula stage at approximately four days.

JAN LANGMAN & T.W. SADLER, LANGMAN'S MEDICAL EMBRYOLOGY 26 (5th ed. 1985); while defining "abnormal zygotes" as:

> Abnormal human and other mammalian zygotes have been frequently described. Of a total of eight zygotes in the preimplantation stage recovered from the uterine tube by Hertig and coworkers, four appeared to be normal, whereas the other four were abnormal. The abnormal zygotes, which varied from three to five days of age, showed multinucleated blastomeres and variable degrees of cellular degeneration. Although it is doubtful that any of these zygotes would have been able to implant, all four were recovered from patients of normal fertility. According to Hertig, 16 per cent of all oocytes coming in contact with sperm are not cleaving, either because they are not properly penetrated by sperm, or the mitotic mechanism is not functioning. Another 15 per cent are lost during the first week at cleavage and blastula stages. Since many abnormal zygotes are lost during the early stages of development, this process is often considered as a "self-cleaning" process, whereby abnormal embryos are eliminated without the mother being aware of it.

JAN LANGMAN, LANGMAN'S MEDICAL EMBRYOLOGY 29 (4th ed. 1981).

D. Law Dictionaries

Black's Law Dictionary defines "embryo" as: "A developing but unborn or unhatched animal; esp., an unborn human from conception until the development of organs (i.e., until about the eighth week of pregnancy)," "embryo formatus" as:

> A human embryo organized into human shape and endowed with a soul. Though rejected in the early doctrine of the Christian church, the distinction between the embryo *formatus* and *informatus* was accepted by Gratian (regarded as the founder of canon law) in his *Decretum* (ca. 1140), in which he said that abortion is not murder if the fetus has not yet been infused with a soul. Though he did not specify the time of formation or animation, by the 16th century canonists accepted that the time of formation and animation was the 40th day after conception for the male fetus and the 80th day for the female.

BLACK'S LAW DICTIONARY 540 (7th ed. 1999). "Embryo informatus" is defined as: "A human embryo before it has been endowed with a soul." *Id*. at 541. *The Sloane-Dorland Annotated Medical-Legal Dictionary*, defines "embryo" as:

> in animals, those derivatives of the fertilized ovum that eventually become the offspring, during their period of most rapid development, i.e., after the long axis appears until all major structures are represented. In man, the developing organism is an embryo from about two weeks after fertilization to the end of seventh or eighth week.

RICHARD SLOANE, THE SLOANE-DORLAND ANNOTATED MEDICAL-LEGAL DICTIONARY 246 (1987).

The new view must incorporate both the wonder and respect deserved by the process that unites sperm and egg, with the recent advances in harnessing the power of the egg to create replacement cells with the potential to alleviate multiple human sufferings.

Such a new view will require compromise by polarized social groups, including some religious faiths. Indeed, it is doubtful that all scientists will agree with the terminology proposed in the last section of this Article. But the overwhelming need to alleviate human suffering is worthy of such compromise.

A. *Legal Definitions by State Law*[34]

Thirty-five states, Arizona,[35] Arkansas,[36] California,[37] Florida,[38] Georgia,[39] Idaho,[40] Illinois,[41] Indiana,[42] Iowa,[43] Kentucky,[44] Louisiana,[45] Maine,[46] Massachusetts,[47] Michigan,[48] Minnesota,[49] Missouri,[50] Montana,[51] Nebraska,[52] New Hampshire,[53] New Jersey,[54] New Mexico,[55] New York,[56]

[34] The information presented herein relates definitions used by states in drafting their legislation. For a comprehensive analysis of state laws relative to human embryo and fetal research, see Lori B. Andrews, *State Regulation of Embryo Stem Cell Research, in* ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, *supra* note 10, at A10 (concluding that "[s]tate lawmakers have expressed their concern for the sanctity of life—and its inherent value—by the laws they have adopted regarding research on conceptuses and commercialization of body tissue").

[35] ARIZ. REV. STAT. ANN. §§ 36-2302 to -2303 (West 2003).

[36] ARK. CODE. ANN. §§ 20-17-801 to -802 (Michie 2000).

[37] CAL. HEALTH & SAFETY CODE §§ 123440, 123445 (West 1996).

[38] FLA. STAT. ANN. § 390.0111(6)-(7) (West 2002).

[39] GA. CODE ANN. §§ 16-12-144(a), -160(a) (Harrison 1998).

[40] IDAHO CODE §§ 18-907(1)(e), -907(2), -907(3) (Michie 1999 & Supp. 2002).

[41] 720 ILL. COMP. STAT. 510/12 (LEXIS through 2003 legislation).

[42] IND. CODE ANN. § 16-34-2-6 (Michie 1993).

[43] IOWA CODE ANN. § 707B.4 (West 2003).

[44] KY. REV. STAT. ANN. § 436.026 (Michie 1999).

[45] LA. REV. STAT. ANN. §§ 9:121-9:133 (West 1991).

[46] ME. REV. STAT. ANN. tit. 22, § 1593 (West 1992).

[47] MASS. ANN. LAWS ch. 112, § 12J (Law. Co-op. 2003).

[48] MICH. COMP. LAWS §§ 333.2685, -2692 (2001).

[49] MINN. STAT. ANN. § 436.026 (West 1998).

[50] MO. ANN. STAT. § 188.037 (West 1996).

[51] MONT. CODE ANN. § 50-20-108(3) (2003).

[52] NEB. REV. STAT. §§ 28-342, -346 (1995).

[53] N.H. REV. STAT. ANN. § 168-B:15 (2001).

[54] N.J. STAT. ANN. § 2C:11A-1 (West, WESTLAW through 2003 legislation).

[55] N.M. STAT. ANN. §§ 24-9A-1 to 24-9A-5 (Michie 2000).

[56] N.Y. PENAL LAW § 125.45 (McKinney, LEXIS through 2003 Sess.).

North Dakota,[57] Ohio,[58] Oklahoma,[59] Pennsylvania,[60] Rhode Island,[61] South Dakota,[62] Tennessee,[63] Texas,[64] Utah,[65] Virginia,[66] Washington,[67] Wisconsin,[68] Wyoming[69] have passed legislation with respect to human fetuses and embryos. Much of the legislation was passed in the early-1980s to regulate the use of fetal tissue for research and/or therapeutic applications.[70] Several states have amended existing legislation, or passed new legislation relative to human cloning.[71] A few states have included definitions of embryo and related terms in their legislation.[72]

[57] N.D. CENT. CODE §§ 14-02.2-01 to -02 (1997).

[58] OHIO REV. CODE ANN. § 2919.14 (Anderson 1996).

[59] OKLA. STAT. ANN. tit. 63, § 1-735 (West 1997).

[60] 18 PA. CONS. STAT. ANN. § 3216 (West 2000).

[61] R.I. GEN. LAWS § 11-54-1 (2002).

[62] S.D. CODIFIED LAWS § 34-23A-17 (Michie 1994).

[63] TENN. CODE ANN. § 39-15-208 (2003).

[64] TEX. PENAL CODE ANN. § 48.02 (Vernon 2003).

[65] UTAH CODE ANN. §§ 76-7-310 to 11 (2003).

[66] VA. CODE ANN. §§ 32.1-289 to -289.1 (Michie 1997).

[67] WASH. REV. CODE ANN. § 9.02.130 (West 2003).

[68] WIS. STAT. ANN. § 940.04 (West 1996).

[69] WYO. STAT. ANN. § 35-6-115 (Michie 2003).

[70] *See, e.g.*, ARK. CODE ANN. § 20-17-802 (2000).

[71] ARK. CODE ANN. §§ 20-16-1001 to -1002 (2000); CAL. HEALTH & SAFETY CODE § 24185 (West Supp. 2004); IOWA CODE ANN. §§ 707B.1, -B.4 (West 2003); LA. REV. STAT. ANN. § 40:1299.36 (West 2001); MICH. COMP. LAWS ANN. § 333.16274 (West 2001); MO. ANN. STAT. § 1.217 (West 2000); N.D. CENT. CODE § 12.1-39-01 (Supp. 2003); R.I. GEN. LAWS § 23-16.4-1 (2001).

[72] See, for example, FLA. STAT. ANN. § 742.13 (West 1997):

(4) "Fertilization" means the initial union of an egg and sperm.

(9) "Implantation" means the event that occurs when a fertilized egg adheres to the uterine wall for nourishment.

(12) "Preembryo" means the product of fertilization of an egg by a sperm until the appearance of the embryonic axis;

IDAHO CODE § 18-907 (Bender, LEXIS through 2003 Sess.):

(2) For purposes of this section the terms "embryo" or "fetus" shall mean any human in utero;

LA. REV. STAT. ANN. § 121 (West 2000):

A "human embryo" for the purposes of this Chapter is an in vitro fertilized human ovum, with certain rights granted by law, composed of one or more living human cells and human genetic material so unified and organized that it will develop in utero into an unborn child

§ 123. Capacity

An in vitro fertilized human ovum exists as a juridical person until such time as the in vitro fertilized ovum is implanted in the womb; or at any other time when rights attach to an unborn child in accordance with law.

§ 124. Legal status

As a juridical person, the in vitro fertilized human ovum shall be given an identification by the medical facility for use within the medical facility which entitles such ovum to sue or be sued. The confidentiality of the in vitro fertilization patient shall be maintained;

N.M. STAT. ANN. § 24-9A-I (Michie 2000):

"[C]onception" means the fertilization of the ovum of a human female by the sperm of a human male;

N.D. CENT. CODE. § 12.1-39-01 (1997):

Historically, the biology of human eggs for the first two weeks after ovulation was unknown, unseen, and untouted. Whether the egg was fertilized, and failed to develop normally, could not be known. Abortion legislation and assisted reproductive technologies forever changed the need to describe and chronicle the immediate events that follow sperm penetration of an egg. The wide range of definitions and descriptions of early human conception presented here reveal the failure of science to provide clear meanings for these developmental stages. As judicial rulings point out, the need for clear descriptions and terminology have been dealt with on a case-by-case basis and have yielded a variety of definitions,[73] and

"Human embryo" means a living organism of the species homo sapiens from the single-celled state to eight weeks' development;

OKLA. STAT. ANN. tit. 63, § 1-730 (West 1997):

(2) "Unborn child" means the unborn offspring of human beings from the moment of conception, through pregnancy, and until live birth including the human conceptus, zygote, morula, blastocyst, embryo and fetus;

(4) "Conception" means the fertilization of the ovum of a female individual by the sperm of a male individual;

S.D. CODIFIED LAWS § 34-14-20 (Michie, LEXIS through 2003 Spec. Sess.):

For purposes of §§ 34-14-16 to 34-14-20, inclusive, the term, human embryo, means a living organism of the species Homo sapiens at the earliest stages of development (including the single-celled stage) that is not located in a woman's body;

VA. CODE ANN. § 20-156 (Michie, LEXIS through 2003 Sess.):

"*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.

[73] Most court cases dealing with embryos refer to a medical dictionary for a definition. The Supreme Court of New Jersey stated that:

> A preembryo is a fertilized ovum (egg cell) up to approximately fourteen days old (the point when it implants in the uterus). *The American Heritage Stedman's Medical Dictionary* 667 (1995). Throughout this opinion, we use the term "preembryo," rather than "embryo," because preembryo is technically descriptive of the cells' stage of development when they are cryopreserved (frozen).

J.B. v. M.B., 783 A.2d 707, 708 n.1 (N.J. 2001). The Court of Appeals of New York stated: "We use the parties' term 'pre-zygotes,' which are defined in the record as 'eggs which have been penetrated by sperm but have not yet joined genetic material.'" Kass v. Kass, 696 N.E.2d 174, 175 n.1 (N.Y. 1998). The Supreme Court of Tennessee analyzed the scientific testimony to reach its holding:

> In the record, and especially in the trial court's opinion, there is a great deal of discussion about the proper descriptive terminology to be used in this case. Although this discussion appears at first glance to be a matter simply of semantics, semantical distinctions are significant in this context, because language defines legal status and can limit legal rights. Obviously, an "adult" has a different legal status than does a "child." Likewise, "child" means something other than "fetus." A "fetus" differs from an "embryo." There was much dispute at trial about whether the four- to eight-cell entities in this case should properly be referred to as "embryos" or as "preembryos," with resulting differences in legal analysis.
>
> One expert, a French geneticist named Dr. Jerome Lejeune, insisted that there was no recognized scientific distinction between the two terms. He referred to the four- to eight-cell entities at issue here as "early human beings," as "tiny persons," and as his "kin." . . .
>
> Dr. LeJeune's opinion was disputed by Dr. Irving Ray King, . . . a medical doctor who had practiced as a sub-specialty in the areas of infertility and reproductive endocrinology for 12 years. . . . He testified that the currently accepted term for the zygote immediately after division is "preembryo" and that this term applies up until 14 days after fertilization. . . . At about 14 days, he testified, the group of cells

> begins to differentiate in a process that permits the eventual development of the different body parts which will become an individual. . . .
>
> . . . .
>
> . . . The stage subsequent to the zygote is cleavage, during which the single initial cell undergoes successive equal divisions with little or no intervening growth. As a result, the product cells (blastomeres) become successively smaller, while the size of the total aggregate of cells remains the same. After three such divisions, the aggregate contains eight cells in relatively loose association . . . [E]ach blastomere, if separated from the others, has the potential to develop into a complete adult. . . . Stated another way, at the 8-cell stage, the developmental singleness of one person has not been established.
>
> Beyond the 8-cell stage, individual blastomeres begin to lose their zygote-like properties. Two divisions after the 8-cell stage, the 32 blastomeres are increasingly adherent, closely packed, and no longer of equal developmental potential. The impression now conveyed is of a multicellular entity, rather than of a loose packet of identical cells.
>
> As the number of cells continues to increase, some are formed into a surface layer, surrounding others within. The outer layers have changed in properties toward trophoblast . . . , which is destined [to become part of the placenta]. The less-altered inner cells will be the source of the later embryo. The developing entity is now referred to as a blastocyst, characterized by a continuous peripheral layer of cells and a small cellular population within a central cavity . . . It is at about this stage that the [normally] developing entity usually completes its transit through the oviduct to enter the uterus.
>
> Cell division continues and the blastocyst enlarges through increase of both cell number and [volume]. The populations of inner and outer cells become increasingly different, not only in position and shape but in synthetic activities as well. The change is primarily in the outer population, which is altering rapidly as the blastocyst interacts with and implants into the uterine wall . . . Thus, the first cellular differentiation of the new generation relates to physiologic interaction with the mother, rather than to the establishment of the embryo itself. *It is for this reason that it is appropriate to refer to the developing entity up to this point as a preembryo, rather than an embryo*. . . .
>
> . . . .
>
> . . . One of the fundamental issues the inquiry poses is whether the preembryos in this case should be considered "persons" or "property" in the contemplation of the law. . . .
>
> The policy of the state on the subject matter before us may be gleaned from the state's treatment of fetuses in the womb . . . . This statutory scheme indicates that as embryos develop, they are accorded more respect than mere human cells because of their burgeoning potential for life. But, even after viability, they are not given legal status equivalent to that of a person already born. . . .
>
> . . . The Supreme Court concluded that "the unborn have never been recognized in the law as persons in the whole sense." . . .
>
> . . . .
>
> . . . We conclude that preembryos are not, strictly speaking, either "persons" or "property," but occupy an interim category that entitles them to special respect because of their potential for human life.

Davis v. Davis, 842 S.W.2d 588, 592-95, 597 (Tenn. 1992) (citations omitted) (footnotes omitted). An interesting 1946 court case in Nebraska that charged the defendant (a physician) with abortion made a clear distinction between "viable" and "nonviable," but not between "embryo" and "fetus" when being charged with "foeticide." Hans v. State, 22 N.W.2d 385, 389 (Neb. 1946) (citations omitted). The defendant appealed the guilty verdict on the grounds it was not a fetus that was aborted, but an embryo, and that Nebraska law section 28-404, R.S. 1943 lacked any reference to "embryocide." *Id*. at 388. Since the statute did not define "foetus" and "vitalized embryo," then "general medical meaning and sense as applied should prevail." *Id*. The defendant entered the following definitions into the court record:

> An embryo is "the rudimentary plant in the seed; the product of conception during its intrauterine existence; its first two weeks constitute the ovum stage; from the end

led to somewhat confused terms in new state laws.[74] Government advisory panels, both in the United States[75] and abroad,[76] are also divided on the

> of the 2nd to the beginning of the 8th week is the embryonal stage, and from the beginning of the 3rd month to the termination of gestation is the fetal stage." *Stedman's Medical Dictionary*, 14th Ed., p. 350.
>
> A foetus (fetus) is defined, "The unborn young of an animal after it has taken form in the uterus; in man, the product of conception from the end of the third month to the moment of birth." *Stedman's Medical Dictionary*, 14th Ed., p. 401.

Id. Judge Messmore disagreed. He held that the distinction between embryo and fetus was irrelevant in the context of a charge of "foeticide." He entered into his opinion definitions of "Foetus" and "Foeticide" from three law references:

> "Foetus. In medical jurisprudence. An unborn child. An infant in ventre sa mere." Black's Law Dictionary, 3rd Ed., p. 794.
>
> [1] Foeticide (feticide) in medical jurisprudence means: "Destruction of the fetus; the act by which criminal abortion is produced." Black's Law Dictionary, 3rd Ed., p. 769. See, also, 1 Beck, Medical Jurisprudence, 288; Guy, Medical Jurisprudence, 133 . . . .

Id. at 388-89. The judge also stated:

> Section 28-404, R.S. 1943, uses the language: ". . . to any pregnant woman with a vitalized embryo, or foetus, at an[y] stage of utero gestation, . . ." The statute making the offense "at any stage of utero gestation" means at any stage during pregnancy. See Edwards v. State, 79 Neb. 251 N.W. 611.

Id. at 389.

[74] *See supra* note 72.

[75] The Human Embryo Research Panel defines "embryo" as "in humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus." NAT'L INST. OF HEALTH, REPORT OF THE HUMAN EMBRYO RESEARCH PANEL D-4 (1994), *available at* http://ospp.od.nih.gov/pdf/VOLUME1_REVISED.PDF (last visited Apr. 16, 2004) (on file with the Connecticut Law Review) [hereinafter HUMAN EMBRYO RESEARCH PANEL]. "Preimplantation embryo" is "the very early, free-floating embryo, from the time the egg is fertilized until implantation in the mother's womb is complete, about 12 to 14 days after fertilization." *Id*. at D-7. "Zygote" is "the single-celled, fertilized egg." *Id*. at D-8. "Preembryo" was not included for definition.

The National Bioethics Advisory Commission defines "embryo" as: "1) the beginning of any organism in the early stages of development, 2) a stage (between the ovum and the fetus) in the prenatal development of a mammal, 3) in humans, the stage of development between the second and eighth weeks following fertilization, inclusive." ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, *supra* note 10, at 85. "Pre-implantation embryo" is "1) the embryo before it has implanted in the uterus, 2) commonly used to refer to *in vitro* fertilized embryos before they are transferred to a woman's uterus." *Id*. at 86. "Zygote" is "1) the cell resulting from the fusion of two gametes in sexual reproduction, 2) a fertilized egg (ovum), 3) the diploid cell resulting from the union of a sperm and an ovum, 4) the developing organism during the first week after fertilization." *Id*. "Preembryo" was not included for definition.

The President's Council on Bioethics defines "embryo" as: 1) "The developing organism from the time of fertilization until significant differentiation has occurred, when the organism becomes known as a fetus, 2) "[a]n organism in the early stages of development." PRESIDENT'S COUNCIL ON BIOETHICS, HUMAN CLONING AND HUMAN DIGNITY: AN ETHICAL INQUIRY 230 (2002), *available at* http://bioethics.gov/reports/cloningreport/pcbe_cloning_report.pdf (last visited Feb. 27, 2004) (on file with the Connecticut Law Review) [hereinafter HUMAN CLONING AND HUMAN DIGNITY]. "Zygote" is "[t]he diploid cell that results from the fertilization of an egg cell by a sperm cell." *Id*. at 233. No definition of either "preembryo" or "pre-implantation embryo" was provided.

[76] In Australia, human embryo research was regulated by the states until 2002. For example, the Human Reproductive Technology Act was instituted in the Western Australia Consolidated Acts in 1991, which allows research on human embryos under tightly regulated guidelines following detailed review of the proposed work. Human Reproductive Technology Act, § 20 (1991) (W. Austl.), *available at* http://www.austlii.edu.au/au/legis/wa/consol_act/hrta1991331/index.html#longtitle (last

definition of basic terms, such as "embryo." Science has an obligation to

visited Feb. 25, 2004) (on file with the Connecticut Law Review). Under the interpretation and application section of the Act, "embryo" is defined as "a live human embryo, in the stage of development which occurs from—(a) the completion of the fertilisation of the egg; or (b) the initiation of parthenogenesis, to the time when, excluding any period of storage, 7 completed weeks of the development have occurred . . ." *Id*. § 3. "Fertilisation," for the purposes of the Act, is "the process that commences at the moment of inclusion of a sperm head within the plasma membrane of an egg, and is completed with the appearance of a two-cell zygote . . ." *Id*. No definition of "preembryo" or "pre-implantation embryo" is provided. The Parliament of Victoria in Australia enacted the Infertility Treatment Act in 1995, which allows regulated research on human embryos, including parthenotes, by an "approved" doctor or scientist, in an appropriate setting, with appropriate review and approval. Infertility Treatment Act, No. 63/1995, §§ 22, 23 (1995) (Vict.), *available at* http://www.ita.org.au/PDFs/95_63ar1.pdf (last visited Feb. 25, 2004) (on file with the Connecticut Law Review). The definitions section defines "embryo" as "any stage of human embryonic development at and from syngamy . . . ." *Id*. § 3. "Syngamy" is "that stage of development of a fertilised oocyte where the chromosomes derived from the male and female pronuclei align on the mitotic spindle . . . ," and "zygote" is "the stages of human development from the commencement of penetration of an oocyte by sperm up to but not including syngamy . . . ." *Id*. "Preembryo" and "pre-implantation embryo" are not defined. In 2002, the Australian Parliament adopted "An Act to regulate certain activities involving the use of human embryos, and for related purposes." Research Involving Human Embryos Act, No. 145 (2002) (Austl.), *available at* http://www.health.gov.au/nhmrc/embryo/pdf/embryact.pdf (last visited Feb. 25, 2004) (on file with the Connecticut Law Review). This Act created a mechanism for licensing research and researchers seeking to study "excess" embryos created by assisted reproduction. *Id*. §§ 9, 20. In the definitions section, "human embryo" is defined as "a live embryo that has a human genome or an altered human genome and that has been developing for less than 8 weeks since the appearance of 2 pro-nuclei or the initiation of its development by other means," and "[f]or the purposes of the definition . . . any period when the development of the embryo is suspended is to be disregarded." *Id*. § 7.

In 1999, the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans took effect in Canada. MED. RES. COUNCIL OF CANADA ET AL., TRI-COUNCIL POLICY STATEMENT: ETHICAL CONDUCT FOR RESEARCH INVOLVING HUMANS (2003) (Can.), *available at* http://www.pre.ethics.gc.ca/english/pdf/TCPS%20June2003_E.pdf (last visited Feb. 25, 2004) (on file with the Connecticut Law Review). The Ethical Conduct Guidelines allow research involving surplus embryos from assisted reproduction only "during the first 14 days after their formation by combination of the gametes." *Id*. § 9, art. 9.4(d). Creating embryos by nuclear transplant into eggs is prohibited. *Id*. § 9, art. 9.5. In regard to research involving human embryos, the Council specifically stated that "[r]esearch where fertilization occurs should be regarded as research on embryos." *Id*. § 9.

In the United Kingdom, the Human Fertilisation and Embryology Act, instituted in 1990, allows for research on human embryos by licensed researchers in licensed research facilities following detailed review of the research to be conducted. Human Fertilisation and Embryology Act, c.37, §§ 2, 11-16 (1990) (U.K.), *available at* http://www.hmso.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm (last visited Feb. 25, 2004) (on file with the Connecticut Law Review). This Act defines "embryo" as "(a) a live human embryo where fertilisation is complete, and (b) references to an embryo include an egg in the process of fertilisation, and, for this purpose, fertilisation is not complete until the appearance of a two cell zygote." *Id*. § 1. A report from the Chief Medical Officer's Expert Group Reviewing the Potential of Developments in Stem Cell Research and Cell Nuclear Replacement to Benefit Human Health recommended that research involving nuclear replacement (discussed in the following section) be allowed to go forward under the licensing arrangements already in place. STEM CELL RESEARCH: MEDICAL PROGRESS WITH RESPONSIBILITY, A REPORT FROM THE CHIEF MEDICAL OFFICER'S EXPERT GROUP REVIEWING THE POTENTIAL OF DEVELOPMENT IN STEM CELL RESEARCH AND CELL NUCLEAR REPLACEMENT TO BENEFIT HUMAN HEALTH 45-46 (2000) (U.K.), *available at* http://www.publications.doh.gov.uk/cmo/progress/stemcellresearch/stemcellreport.pdf (last visited Feb. 28, 2004) (on file with the Connecticut Law Review). Attempts to clone a human being are not permitted. *Id*. at 47.

society to rectify this failing and clarify the biological terms so society and legislators can craft informed operational guidelines.

IV. ASSISTED REPRODUCTIVE TECHNOLOGIES

A. *Early Research*

In 1944, the first report of fertilization of a human egg in a laboratory appeared in *Science* from a research team at the Free Hospital for Women in Brookline, Massachusetts.[77] In retrospect, the laboratory conditions employed suggest the eggs may have activated parthenogenically, rather than by fertilization.

In 1969, the first documentation of sperm penetration of a human egg was published.[78] But it would be nearly another decade before a successful pregnancy was reported;[79] Louise Brown, the first successful in vitro fertilized ("IVF") baby, was born in England in 1978.[80] The following year, the National Institutes of Health ("NIH") Ethical Advisory Board ("EAB"), which was formed in 1975, rendered an opinion about research on fertilized human eggs.[81] No action was taken by the NIH about the report or its recommendations, and no other EAB was commissioned after 1980.

In 1981, the first IVF baby was born in the United States.[82] No EAB was created. This created a remarkable limbo with respect to government funding for human IVF research. In 1974, Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[83] The Commission's conclusions and recommendations provided the basis for the core regulations in the Federal Policy for the Protection of Human Subjects.[84] The need for the regulations had been fueled by fetal tissue experimentation, which held promise for several areas of human health, but had alerted the public to

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[77] John Rock & Miriam Menkin, *In Vitro Fertilization and Cleavage of Human Ovarian Eggs*, 100 SCIENCE 105, 105 (1944).

[78] B.D. Bavister et al., *Identification of the Midpiece and Tail of the Spermatozoon During Fertilization of Human Eggs* in Vitro, 20 J. REPROD. & FERTILITY 159, 159-60 (1969).

[79] RealAudio Media File: The Fertility Race—From Barren to Infertile, broadcast by public radio (Nov. 11, 1997), *at* http://news.minnesota.publicradio.org/features/199711/20_smiths_fertility/common/radio.shtml (last visited Apr. 17, 2004) (on file with the Connecticut Law Review) [hereinafter Fertility Race].

[80] *Id*.

[81] Notices, 44 Fed. Reg. 35,033 (June 18, 1979).

[82] Fertility Race, *supra* note 79.

[83] BELMONT REPORT, *supra* note 8.

[84] Subpart A embodies the Common Rule for human subjects research. 45 C.F.R. § 46 (1977). Subpart B covers research on special populations of research subjects: 1) the fetus, 2) pregnant women, and 3) human in vitro fertilization. *Id*.

possible abuses.

> No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.[85]

Ironically, this paragraph in the subpart of the federal guidelines designed to protect the interests of fetuses and pregnant women created a research moratorium for the emerging clinical specialty of assisted reproduction because there effectively was no EAB.[86] The pregnant women and fetuses created by assisted reproduction were, therefore, specifically denied the benefit of federal research dollars by the very federal law codified to protect them.

In many respects, it was a ruse. The NIH accepted grant applications from scientists wishing to study fertilized human eggs.[87] Those applications were submitted for peer review in parallel with all other requests for funding: they were assigned to an Initial Review Group, and at least two scientists were required to review and critique the applications and assign them a merit score based on several criteria, including sound scientific basis, importance of the research to human health, and the resources available to carry out the work. All the while, there was no hope that awards would actually be funded. Hence, the scientists preparing the grant application, which requires intensive literature research, conducting pilot experiments, complying with institutional human subjects review requirements, and amassing a scientific team and all their credentials to demonstrate the work will be done by competent individuals, labored in vain—as did their peer reviewers. This situation persisted for eighteen years.

Throughout the late-1980s, regulatory bodies for assisted reproduction were being established in other countries, such as the United Kingdom and Australia, but U.S. scientists did not effectively lobby for the needed public

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[85] 45 C.F.R. § 46.204(d) (1977).

[86] *See* 44 Fed. Reg. 35,057. The EAB, although formally in existence, concluded that "[t]he Board finds it acceptable . . . for the department to support or conduct research involving human *in vitro* fertilization and embryo transfer," yet "decided not to address the question of the level of funding, if any, which such research might be given." *Id*. Furthermore, as a predicate to the consideration of research proposals, the EAB required that "[a]ll interested parties and the general public . . . be advised if evidence begins to show that the procedure entails risks of abnormal offspring higher than those associated with normal human reproduction." *Id*. This requirement made it impossible to receive funding because evidence of "abnormal" risk cannot exist until research has taken place, but research cannot occur until funding has been awarded.

[87] Oliver H. Lowry, *How to Succeed in Research Without Being a Genius*, 59 ANN. REV. BIOCHEM. 1, 21 (1990).

debate to clarify the need for basic research for infertile women and their in vitro-derived babies. Nor did they develop new terms to describe the new laboratory technologies. Existing terminology was simply stretched to cover the needs. In retrospect, this lack of political activism on the part of U.S. scientists has led to the current rancor and suspicion being leveled at stem cell research.

In addition, when 45 C.F.R. § 46.204(d) was rescinded, it was done quietly, without public or congressional debate. It was simply nullified by section 121(c) of the NIH Revitalization Act of 1993.[88] Almost overnight, § 46.204(d) disappeared altogether.[89] On July 22, 1994, Gary Ellis, Ph.D., Director of the Office for Protection of Research Risks, sent a "Dear Colleague" letter to institutional officials and Institutional Review Board Chairs throughout the country informing them ". . . that research applications and proposals involving in vitro fertilization of human ova may now be submitted to and funded by HHS components without the prior review and advice of a national advisory body."[90]

B. *The Human Embryo Research Panel, 1993-1994*

In the meantime, Dr. Harold Varmus, the Acting Director of NIH, had asked the Assistant Secretary for Health for approval to establish a broad-based panel as a subcommittee of the Advisory Committee to the Director to recommend guidelines for funding preimplantation embryo[91] research. The charge of the Panel was to

> consider various areas of research involving the ex utero preimplantation human embryo and to provide advice as to

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[88] Pub. L. No. 103-43, 107 Stat. 122, 133 (1993).

[89] The Department of Health and Human Services stated:

> HHS is rescinding paragraph (d) of section 204 now so that the regulations will accurately reflect the statutory nullification of the requirement for Ethical Advisory Board review of research involving the in vitro fertilization of human ova, as a prerequisite for funding by HHS and its components.
>
> Notice, public comment, and delayed effective date have been waived for this amendment based on a finding of good cause. These procedures for ensuring public participation in the rulemaking process and time for compliance are unnecessary because the substantive change has already been made by Public Law 103-43. Furthermore, it is a change that relieves a restriction on the funding of research by HHS and its components.

Health & Human Services Policy for Protection of Human Subjects Research, 59 Fed. Reg. 28,276 (June 1, 1994).

[90] Letter from Gary B. Ellis, Ph.D., Director, Office for Protection from Research Risks, "Dear Colleague" (July 22, 1994), *available at* http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc94-03.htm (last visited Mar. 24, 2004) (on file with the Connecticut Law Review).

[91] In a glossary appended to the report of the Human Embryo Research Panel, "embryo" is defined as: "[I]n humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a fetus." HUMAN EMBRYO RESEARCH PANEL, *supra* note 75, at D-4. "Preimplantation embryo" is defined as: "[T]he very early, free-floating embryo, from the time the egg is fertilized until implantation in the mother's womb is complete, about 12 to 14 days after fertilization." *Id*. at D-7.

> those areas that (1) are acceptable for Federal funding, (2) warrant additional review, and (3) are unacceptable for Federal support. For those areas of research considered acceptable for Federal funding, the Panel was asked to recommend specific guidelines for the review and conduct of this research.[92]

After five public, two-day meetings, the Panel[93] deliberated and reported research recommendations in three areas: recommended for federal funding,[94] recommended for further consideration,[95] and not recommended for federal funding.[96]

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[92] *Id*. at ix.

[93] The panel was comprised of: Chair: Steven Muller, Ph.D., President Emeritus, The John Hopkins University; Co-Chair, Policy: Patricia King, J.D., Professor of Law, Georgetown University Law Center; Co-Chair, Science: Brigid Hogan, Ph.D., Professor of Cell Biology, Vanderbilt University School of Medicine; Members: Diane Aronson, RESOLVE; R. Alta Charo, J.D., University of Wisconsin; Patricia Donahoe, M.D., Massachusetts General Hospital; John Eppig, Ph.D., The Jackson Laboratory; Ronald Green, Ph.D., Dartmouth College; Fernando Guerra, M.D., Department of Health, San Antonio, TX; Andrew Hendrickx, Ph.D., University of California, Davis; Mark Hughes, M.D., Ph.D., Baylor College of Medicine; Ola Huntley, Ed.D., Sickle Cell Self-Help Group, CA; Nannerl Keohane, Ph.D., President, Duke University; Bernard Lo, M.D., University of California, San Francisco; Mary Martin, M.D., University of California, San Francisco; Thomas Murray, Ph.D., Case Western Reserve University, School of Medicine; Dorothy Nelkin, New York University; Kenneth Ryan, M.D., Harvard University School of Medicine; Carol Tauer, Ph.D., College of St. Catherine.

[94] Acceptable for Federal Funding:

1. Studies aimed at improving the likelihood for a successful outcome for a pregnancy.
2. Research on the process of fertilization.
3. Studies on egg activation and the relative role of paternally derived and maternally derived genetic material in embryo development (parthenogenesis without transfer).
4. Studies in oocyte maturation or freezing followed by fertilization to determine developmental and chromosomal normality.
5. Research involving preimplantation genetic diagnosis with and without transfer.
6. Research involving the development of embryonic stem cells but only with embryos resulting from IVF treatment for infertility or clinical research that have been donated with the consent of the progenitors.
7. Nuclear transplantation into an enucleated, fertilized or unfertilized (but activated) egg without transfer with the aim of circumventing or correcting an inherited cytoplasmic defect. HUMAN EMBRYO RESEARCH PANEL, *supra* note 75, at 75-76.

[95] Research that Warrants Additional Review:

1. Cloning by blastomere separation or blastocyst splitting without transfer.
2. Research between the appearance of the primitive streak and the beginning of closure of the neural tube.
3. Research that uses fetal oocytes for fertilization without transfer or for parthenogenesis.
4. Nuclear transplantation into an enucleated, fertilized or unfertilized (but activated) egg with transfer for the purpose of circumventing or correcting an inherited cytoplasmic defect.
5. Embryonic stem cell research that uses deliberately fertilized oocytes. *Id.* at 77-79. Carol A. Tauer included a dissenting statement that this research should be considered unacceptable for federal funding. *Id.* at B-3.

[96] Research Considered Unacceptable for Federal Funding:

1. Cloning of human preimplantation embryos by separating blastomeres or dividing blastocysts (induced twinning), followed by transfer to the uterus.

Two types of acceptable research were singled out for special consideration. One was research involving the use of leftover embryos from an infertility program where one of the progenitors was an anonymous gamete source who received monetary compensation. This research was specifically objected to by one member of the Panel.[97] The other was research involving the fertilization of eggs where it is necessary for the validity of a study that is potentially of outstanding scientific and therapeutic value. This research was specifically objected to by another member of the Panel.[98]

In addition to these recommendations, the Panel recommended against the formation of a standing EAB constituted specifically for the purpose of reviewing research protocols involving embryos and fertilized eggs. Instead, the Panel recommended:

> [T]hat all research proposals involving preimplantation human embryo research that are submitted to NIH for funding or that are proposed for conduct in the NIH intramural research program be subject to an additional review at the national level by an ad hoc body created with the discretionary authority of the Director of NIH.[99]

The Panel submitted its report to the Advisory Committee in September 1994. The Advisory Committee formally approved the Panel's recommendations and transmitted them to Dr. Varmus on December 1, 1994, six months after 45 C.F.R. § 46.204(d) was rescinded.[100] In a surprise decision, President Clinton declared on December 2, 1994, before Dr. Varmus had an opportunity to respond:

> The Director of the National Institutes of Health has received a recommendation regarding federal funding of research on human embryos. The subject raises profound

2. Studies designed to transplant nuclei into an enucleated egg, including nuclear cloning, in order to duplicate a genome or to increase the number of embryos with the same genotype with transfer.

3. Research beyond the onset of closure of the neural tube.

4. Research involving the fertilization of fetal oocytes with transfer.

5. Preimplantation genetic diagnosis for sex selection except for sex-linked genetic diseases.

6. Development of human-nonhuman and human-human chimeras with or without transfer.

7. Cross-species fertilization except for clinical tests of the ability of sperm to penetrate eggs.

8. Attempted transfer of parthenogenetically activated human eggs.

9. Attempted transfer of human embryos in nonhuman animals for gestation.

10. Transfer of human embryos for extrauterine or abdominal pregnancy. *Id.* at 80-83.

[97] *Id.* at C-3.

[98] *Id.* at A-3.

[99] *Id.* at 72.

[100] National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43, § 121c (codified at 42 U.S.C. § 289g (2000)).

> ethical and moral questions as well as issues concerning the appropriate allocation of federal funds. I appreciate the work of the committees that have considered this complex issue and I understand that advances in in vitro fertilization research and other areas could derive from such work. However, I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research . . . .[101]

Dr. Varmus interpreted this opinion to mean that research on surplus human embryos left over from fertility procedures would still be eligible for federal funding.[102] But this possibility was essentially eliminated by a congressional rider attached to that year's NIH budget that none of the funds appropriated could be used to support any activity involving:

> 1) the creation of a human embryo or embryos for research purposes; or 2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 C.F.R. 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 USC 289g(b)).[103]

To this day, the ban on federal funding of research on fertilized human eggs has been continually renewed by the rider attached to the budget appropriations for the NIH. The topic has not been publicly debated nor formally debated in both houses of Congress.

C. *Eggs Activated Without Sperm*

The next scientific advance to rock the reproductive technology community was the cloned sheep, Dolly, announced in 1997[104] followed quickly by the cloned cow, Amy.[105]

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[101] Statement on Federal Funding of Research on Human Embryos, 1994 PUB. PAPERS 2142 (Dec. 2, 1994), *available at* http://clinton6.nara.gov/1994/12/1994-12-02-president-on-nih-and-human-embryo-research.html (last visited Apr. 17, 2004) (on file with the Connecticut Law Review).

[102] Robin Alta Charo, *The Hunting of The Snark: The Moral Status of Embryos, Right-to-Lifers, and Third World Women*, 6 STAN. L. & POL'Y REV. 11, 14 (1995).

[103] Balanced Budget Downpayment Act, I, Public Law No. 104-99, § 128, 110 Stat. 26, 34 (1996).

[104] Wilmut et al., *supra* note 6, at 810.

[105] *Bovine Telomere*, *supra* note 7.

1. *Nuclear Transplants*

As discussed previously, to test the ability of eggs to remodel chromosomes other than those in sperm heads, and to test the capacity of chromosomes from a variety of cell types to support development, technologies were developed to remove the egg's chromosomes and then transplant a nucleus to be tested into the egg's cytoplasm. This procedure addressed several corollary questions as well: Can the egg remodel foreign chromosomes without its own? Can the egg replicate the foreign chromosomes and initiate cell division without sperm? Once the egg-dependent cleavages are accomplished, can the transplanted, remodeled nucleus direct expression of its genes to continue development? The birth of Dolly the sheep provided a "Yes" answer to each of these questions with the important caveat that the "Yes" applied to only one in 250 of the reconstructed eggs. The remarkably low success rate for this procedure, once it worked at all, remains a puzzle.

Figure 3[106]

The success of Dolly the sheep and Amy the cow by this technology overturned at least twenty-three years of reproductive biology dogma, embodied in the sentence: "Differential activity of maternal and paternal genomes . . . suggest that the cloning of mammals by simple nuclear transfer is biologically impossible."[107] Finally, after years of experiments, the scientific community had established without doubt that the prevailing dogma was in error and that at least some differentiated cells contain the same genetic information as pluripotent, embryonic cells, and at least some eggs had the capacity to fully de-differentiate somatic cell nuclei. It was widely recognized within the scientific community that even more

[106] KIESSLING & ANDERSON, *supra* note 16. Reprinted with permission from Jones and Bartlett Publishers, Sudbury, MA, www.jbpub.com.

[107] James McGrath & Davor Solter, *Inability of Mouse Blastomere Nuclei Transferred to Enucleated Zygotes to Support Development in Vitro*, 226 SCIENCE 1317, 1319 (1984).

important than the ability to clone animals was the ability to create pluripotent stem cells for therapeutic purposes.

The need for new terminology intensified as the public grappled with the concept that the technology to create replacement cells for tissues in need, such as dying heart muscle, dying neurons, dying insulin-producing cells, and dying kidney cells, diseases estimated to affect half the population of the United States,[108] could also be used to clone a human. Nowhere in the world was the public debate more rancorous than in the United States, perhaps because neither the public nor Congress had had the opportunity to debate the value of conducting research on fertilized human eggs. Other countries, such as England, Australia and the Scandinavian countries had already been through the public debates about the importance of studying fertilized human eggs and had guidelines in place for the research. The only guidelines in place in the United States was the moratorium on allocation of NIH research dollars to studies of ". . . 1) the creation of a human embryo or embryos for research purposes; or 2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death . . . ."[109]

2. *Parthenogenesis*

Eggs can undergo activation and cleavage without sperm. Termed "parthenogenesis," after the Greek word for virgin, spontaneous human egg activation has been recognized for many years, as evidenced by the appearance of dermoid cysts in the ovary.[110] In addition, benign tumors, "teratomas,"[111] that can contain multiple types of differentiated cells are thought to arise spontaneously from eggs.

Figure 4[112]

[108] Daniel Perry, *Patients' Voices: The Powerful Sound in the Stem Cell Debate*, 287 SCIENCE 1423, 1423 (2000).

[109] Balanced Budget Downpayment Act, I, Public Law No. 104-99, § 128, 110 Stat. 26, 34 (1996).

[110] For a comprehensive overview of ovarian cysts, see Women's Health Concern, *Fact Sheet 15*, *available at* www.womens-health-concern.org/leaflets/ov_cysts.htm (last visited Apr. 17, 2004) (on file with the Connecticut Law Review).

[111] ScienceDaily defines "teratoma" as: "[A] type of tumour that derives from pluripotent germ cells." *See* ScienceDaily Encyclopedia *at* http://www.sciencedaily.com/encyclopedia/teratoma (last visited Apr. 17, 2004) (on file with the Connecticut Law Review).

[112] KIESSLING & ANDERSON, *supra* note 16. Reprinted with permission from Jones and Bartlett Publishers, Sudbury, MA, www.jbpub.com.

Laboratory methods have been available for many years to activate mature eggs without sperm. Brief exposure to chemicals that incite the release of stores of calcium ions within the egg cytoplasm, followed by exposure to inhibitors of the enzymes known to maintain chromosomes in a condensed state, bring about retention of a diploid set of chromosomes within a single pronucleus, followed by the initiation of cleavage divisions that can proceed to the blastocyst stage. Since important early events that follow penetration by sperm, such as duplication of the chromosomes, appear to be egg functions, parthenogenesis provides a valuable system for studying cleavage stage eggs without creating embryos. The value of such a system was pointed out by the Human Embryo Research Panel.[113]

Unless parthenotes themselves are considered embryos. The potential for parthenotes to develop to offspring is controversial and has never been reported for mammals. Interestingly, parthenotes are deficient in placental formation, supporting the concept that paternal genes are important in the derivation of the placenta.[114] As will be discussed below, this may be of actual advantage to the derivation of stem cells from parthenotes.

3. *Parthenote Stem Cells*

Monkey parthenotes have been shown to give rise to pluripotent stem cells.[115] Monkey eggs were activated in the laboratory with chemicals to

[113] HUMAN EMBRYO RESEARCH PANEL, *supra* note 75, at 76.

[114] Tomohiro Kono et al., *Mouse Parthenogenetic Embryos with Monoallelic H19 Expression Can Develop to Day 17.5 of Gestation*, 243 DEVELOPMENTAL BIOLOGY 294, 294 (2002).

[115] Jose B. Cibelli et al., *Parthenogenetic Stem Cells in Nonhuman Primates*, 295 SCIENCE 819, 819 (2002).

mimic the stimulation of the eggs by sperm entry, as described previously.

Figure 5[116]

Unlike the events immediately after sperm entry that lead to extrusion of half the egg's chromosomes, the enzyme inhibitors maintain the egg chromosomes so both copies of the twenty-three pairs are enclosed within the single, large pronucleus. Thus, the parthenote is diploid. Monkey egg cleavage was successful to the blastocyst stage; ICMs were isolated and used to generate stem cells. These cells have now been studied by several investigators throughout the country and shown to give rise to a variety of cell types.[117]

An attempt to derive pluripotent stem cells from human parthenotes was reported in 2001.[118] Human eggs were readily activated by brief exposure to the same chemicals used for the monkey eggs, and a relatively high percentage developed to blastocysts, but no parthenote stem cells were successfully derived.

[116] Diagram by Ann A. Kiessling.

[117] Kent Vrana et al., *Nonhuman Primate Parthenogenic Stem Cells*, 100 PROC. NAT'L ACAD. SCI. 11911, 11913 (2003).

[118] Jose B. Cibelli et al., *Somatic Cell Nuclear Transfer in Humans: Pronuclear and Early Embryonic Development*, 2 J. REGENERATIVE MED. 25, 28-29 (2001).

D. *National Bioethics Advisory Commission, 1998-1999*[119]

On November 14, 1998, President Clinton wrote to Dr. Shapiro, Chair of the National Bioethics Advisory Commission:

> Dear Dr. Shapiro:
> This week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week, and to report back to me as soon as possible. [120]

The President referred to a report in the *New York Times* that a scientist at a private company in Massachusetts had transferred human nuclei into a cow egg with its nucleus removed.[121] The *New York Times* report followed on the heels of two scientific reports of the derivation of human stem cells, the first from fetal germ cells,[122] termed "embryonal germ cells," and the second from leftover human blastocysts,[123] termed "embryonic stem cells." Because of the federal moratorium on support of such research, both scientists conducted their research in privately funded facilities separate from university research laboratories which received funding from the NIH.

Dr. Shapiro's response to President Clinton's request was to discuss

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[119] Commissioners involved in all deliberations of the Ethical Issues in Human Stem Cell Research: Harold Shapiro, Ph.D., President, Princeton University, Chair; Patricia Backlar, Oregon Health Sciences University; Arturo Brito, M.D., University of Miami School of Medicine; Alexander Morgan Capron, L.L.B., University of Southern California; Eric J. Cassell, M.D., Cornell University Medical College; James F. Childress, Ph.D., University of Virginia; David Cox, M.D., Ph.D., Stanford University School of Medicine; Rhetaugh Graves Duman, Ph.D., R.N., University of Michigan; Laurie M. Flynn, National Alliance for the Mentally Ill; Steven Holtzman, Millennium Pharmaceuticals; Bette O. Kramer, Richmond Bioethics Consortium; Bernard Lo, M.D., University of California, San Francisco; Lawrence Miike, M.D., J.D., Kaneohe, Hawaii; Thomas Murray, Ph.D., The Hastings Center; Diane Scott-Jones, Ph.D., Temple University. 1998-1999 NAT'L BIOETHICS ADVISORY COMM'N BIENNIAL REP. at v, *available at* http://www.georgetown.edu/research/nrcbl/nbac/pubs/Biennial98-99.pdf [hereinafter BIENNIAL REP.].

[120] ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, *supra* note 10, at 90.

[121] Michael West, CEO of Advanced Cell Technology, informed the reporter about preliminary pilot experiments designed to test the utility of cow eggs, far less precious than human eggs, to remodel human nuclei. The work established that cow eggs were not useful in this regard. Nicholas Wade, *Researchers Claim Embryonic Cell Mix of Human and Cow*, N.Y. TIMES, Nov. 12, 1998, at A1.

[122] Michael J. Shamblott et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, 95 PROC. NAT'L ACAD. SCI. 13726, 13726 (1998), *available at* http://www.pnas.org/cgi/reprint/95/23/13726.pdf.

[123] J.A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145, 1145 (1998).

the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg at its November meeting.[124] Also present at the meeting was Dr. Michael West, President and CEO of Advanced Cell Technology, the Massachusetts company that revealed the human-cow egg experiment to the *New York Times* reporter. To frame the most pressing issues at hand, the Commissioners considered three questions:

> 1. Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?
>
> 2. Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?
>
> 3. If the fusion of a human cell and the egg of a non-human animal does not result in an embryo with the potential to develop into a child, what ethical issues remain?[125]

The Commission determined that there was insufficient scientific evidence to answer questions one and two, with much of the controversy revolving around the definition of embryo. If the answers to questions one and two were No, then the Commission reasoned no new ethical issues arose from the research. Clearly, the technology required additional consideration.

Subsequently, the Commission considered the ethical issues in human stem cell research at length. In September, 1999, the Commission released its report.[126] On the whole, the report is a balanced and comprehensive review of the science and ethics surrounding human embryo research and stem cell research. There is a considerable effort to accurately represent the science, the limitations of relevant language, the potential therapeutic value of stem cells, and the legal framework in place for federal support of human embryonic stem cell research. In addition, testimony presented to the Commission by a wide cross-section of individuals from the public, private, and religious sectors, and papers commissioned, created the most complete and balanced public debate in the United States to date in the general area of human embryo research. The report is notably silent with respect to research involving human parthenotes.

Through its deliberations, the Commission arrived at thirteen recommendations. These recommendations focused on: embryonal germ

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[124] ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, *supra* note 10, at 90-91.

[125] *Id*.

[126] *Id*. at 1.

("EG") cells from fetal tissue;[127] embryonic stem ("ES") cells from embryos remaining after infertility treatments,[128] ES cells from embryos made solely for research purposes using IVF,[129] ES cells from embryos made using somatic cell nuclear transfer into oocytes,[130] requirements for donation to stem cell research of embryos that would otherwise be discarded after infertility treatment,[131] no promises to embryo donors that stem cells will be provided to particular patient-subjects,[132] commerce in embryos and cadaveric fetal tissue,[133] creation and duties of an oversight and review panel,[134] institutional review of protocols to derive stem cells,[135]

[127] "Research involving the derivation and use of human EG cells from cadaveric fetal tissue should continue to be eligible for federal funding. Relevant statutes and regulations should be amended to make clear that the ethical safeguards that exist for fetal tissue transplantation also apply to the derivation and use of human EG cells for research purposes." ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, *supra* note 10, at EXECUTIVE SUMMARY 3.

[128] "Research involving the derivation and use of human ES cells from embryos remaining after infertility treatments should be eligible for federal funding. An exception should be made to the present statutory ban on federal funding of embryo research to permit federal agencies to fund research involving the derivation of human ES cells from this source under appropriate regulations that include public oversight and review." *Id*. at 4.

[129] "Federal agencies should *not* fund research involving the derivation or use of human ES cells from embryos made solely for research purposes using IVF." *Id*. at 5 (emphasis added).

[130] "Federal agencies should *not* fund research involving the derivation or use of human ES cells from embryos made using somatic cell nuclear transfer into oocytes." *Id*. (emphasis added).

[131] "Prospective donors of embryos remaining after infertility treatments should receive timely, relevant and appropriate information to make informed and voluntary choices regarding disposition of the embryos. Prior to considering the potential research use of the embryos, a prospective donor should have been presented with the option of storing the embryos, donating them to another woman, or discarding them. If a prospective donor chooses to discard embryos remaining after infertility treatment, the option of donating to research may then be presented." *Id*. at 6. Detailed recommendations for the nature of the information presented to prospective embryo donors are included in ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH, *supra* note 10, at EXECUTIVE SUMMARY.

[132] "In federally funded research involving embryos remaining after infertility treatments, researchers may not promise donors that ES cells derived from their embryos will be used to treat patient-subjects specified by the donors." *Id*. at 7.

[133] "Embryos and cadaveric fetal tissue should not be bought or sold." *Id*.

[134] "DHHS [Department of Health & Human Services] should establish a National Stem Cell Oversight and Review Panel to ensure that all federally funded research involving the derivation and/or use of human ES or EG cells is conducted in conformance with the ethical principles and recommendations contained in this report." *Id*.

[135] "Protocols involving the derivation of human ES and EG cells should be reviewed and approved by an IRB or by another appropriately constituted and convened institutional review body prior to consideration by the National Stem Cell Oversight and Review Panel. This review should ensure compliance with any requirements established by the panel, including confirming that individuals or organizations (in the United States or abroad) that supply embryos or cadaveric fetal tissue have obtained them in accordance with the requirements established by the panel." *Id.* at 8.

sponsoring agency review of research use of stem cells,[136] voluntary actions by private sponsors of research that would be eligible for federal funding,[137] voluntary actions by private sponsors of research that would not be eligible for Federal funding,[138] and sunset provision for National Panel.[139] The recommendations of the National Bioethics Advisory Commission were not adopted by the federal government; following the election of George W. Bush to the presidency in 2000, the charter of the Commission was not renewed.

E. *President's Council on Bioethics*

The President's Council on Bioethics ("Council") was created on November 28, 2001 with the mission:

> [T]o undertake fundamental inquiry into the human and moral significance of developments in biomedical and behavioral science and technology;
>
> [T]o explore specific ethical and policy questions related to these developments;
>
> [T]o provide a forum for a national discussion of bioethical issues;
>
> [T]o facilitate a greater understanding of bioethical issues; and
>
> [T]o explore possibilities for useful international collaboration on bioethical issues. [140]

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[136] "All federal agencies should ensure that their review processes for protocols using human ES or EG cells comply with any requirements established by the National Stem Cell Oversight and Review Panel, paying particular attention to the adequacy of the justification for using such cell lines." *Id.* at 9.

[137] "For privately funded research projects that involve ES or EG cells that would be eligible for federal funding, private sponsors and researchers are encouraged to adopt voluntarily the applicable recommendations of this report. This includes submitting protocols for the derivation of ES or EG cells to the National Stem Cell Oversight and Review Panel for review and cell line certification." *Id.* at 9-10.

[138] "For privately funded research projects that involve deriving ES cells from embryos created solely for research purposes and that are therefore not eligible for federal funding . . .

a) professional societies and trade associations should develop and promulgate ethical safeguards and standards consistent with the principles underlying this report, and

b) private sponsors and researchers involved in such research should voluntarily comply with these safeguards and standards." *Id.* at 10.

[139] "The National Stem Cell Oversight and Review Panel should be chartered for a fixed period of time, not to exceed five years. Prior to the expiration of this period, DHHS should commission an independent evaluation of the panel's activities to determine whether it has adequately fulfilled its functions and whether it should be continued." *Id.*

[140] Exec. Order No. 13,237, 66 Fed. Reg. 59,851 (Nov. 28, 2001).

The Council commenced deliberations on the topic of human cloning at its first meeting in January, 2002, and continued the discussion at its February, April, and June meetings. All told, the Council held twelve ninety-minute conversations on the subject. The report of the Council, "Human Cloning and Human Dignity: An Ethical Inquiry," devoted an entire chapter to the importance of accurate terminology.[141] It eschewed the use of terms that appeared in the popular press, such as "therapeutic cloning" and SCNT for "somatic cell nuclear transfer" and highlighted the importance of accurate terminology for the decision making process, especially to the non-scientist.

The Council arrived at two possible policy alternatives, each supported by a portion of the Council Members.

Majority Recommendation[142]

Ten members of the Council recommend a ban on cloning-to-produce-children combined with a four-year moratorium on cloning-for-biomedical-research.[143] They also call for a federal review of current and projected practices of human embryo research, pre-implantation genetic diagnosis, genetic modification of human embryos and gametes, and related matters, with a view to recommending and shaping ethically sound policies for the entire field.

Minority Recommendation[144]

Seven members of the Council recommend a ban on cloning-to-produce-children, with regulation of the use of cloned embryos for

[141] HUMAN CLONING AND HUMAN DIGNITY, *supra* note 75, at ch. 3.

[142] Supported by Rebecca Dresser, J.D., M.S., Washington University Schools of Law and Medicine; Francis Fukuyama, Ph.D., Johns Hopkins University; Robert George, Ph.D., J.D., Princeton University; Mary Ann Glendon, J.D., M.L., Harvard University; Alfonso Gomez-Lobo, Ph.D., Georgetown University; William Hurlbut, M.D., Stanford University; Leon Kass, M.D., Ph.D., University of Chicago; Charles Krauthammer, M.D., Syndicated Columnist; Paul McHugh, M.D., Johns Hopkins School of Medicine; and Gilbert Meilaender, Ph.D., Valparaiso University. *Id.* at 5.

[143] A note of clarity needs to be added here with respect to twinning. A group of investigators divided fertilized human eggs in two, either at the early cleavage stage, or at somewhat later stages, and referred to them as "clones." Rebecca Kolberg, *Human Embryo Cloning Reported*, 262 SCIENCE 652, 652 (1993). A similar set of experiments was reported for monkey embryos. G. P. Schatten, *Clonal Propagation of Primate Offspring by Embryo Splitting*, 287 SCIENCE 317, 317 (2000). The more accurate term for such procedures is twinning, not cloning. Even though they are clones of each other, the most common interpretation of the word "clone" by the lay public is genetic replication of an adult.

[144] Supported by Elizabeth Blackburn, Ph.D., D.Sc., University of California San Francisco; Daniel Foster, M.D., University of Texas Southwestern Medical School; Michael Gazzaniga, Ph.D., Dartmouth College; William May, Ph.D., Southern Methodist University; Janet Rowley, M.D., D.Sc., Pritzker School of Medicine, University of Chicago; Michael Sandel, Ph.D., Harvard University; and James Wilson, Ph.D., University of California Los Angeles. HUMAN CLONING AND HUMAN DIGNITY, *supra* note 75, at 13.

biomedical research.

The two recommendations clearly reflect the uncertain nature and moral standing of "embryos" created following nuclear transplantation into an egg. The report was transmitted to President Bush on July 10, 2002, nearly three months after he publicly announced his decision to not allow federal funds to support the derivation of human embryonic stem cells by any means, but to allow support for studies of the stem cell lines that had been derived around the world prior to April, 2002.

F. Summary

The clear limit imposed on human reproduction is the human egg. Few in number, powerful in nature, the human egg is at the heart of the controversy surrounding human embryo research, human cloning, and the derivation of human embryonic stem cells for therapeutic purposes. Prior to the advent of human assisted reproductive technologies, the activities of the human egg for the first two weeks following its release from the ovary into the female reproductive tract could not be known. If not fertilized, or not developing normally, it simply disappeared and was not mourned. Only when it signaled the mother that it was developing into an embryo was its presence and whereabouts known with certainty.

The advent of assisted reproductive technologies changed all that. Eggs could be viewed from the moment of their collection from the ovary. Their two weeks of private solitude no longer existed. Given their precious nature, and their intrinsic value to the couple hoping to parent, the loss of each and every egg was mourned. No longer did defective fertilization or early development go unnoticed. Society now could witness more than it was prepared for. The moral, ethical, legal and religious status of cleaving eggs needed to be debated by societies sensitive to the need to defend those that cannot defend themselves.

Unfortunately, scientists did not jump into the debate with the clear message that cleaving eggs are not embryos, not yet. Because a natural part of the biology involves checks and balances, essential early steps must proceed as required for the cleaving egg to become an embryo. No new terms were developed in the early days of human assisted reproduction to describe the events that could now be seen in petri dishes that had never been seen before. Scientists were aware of the naturally limited developmental potential of each early conceptus, but society was not aware.

This confusion extends to this day and is now compounded by the new tasks eggs are being called upon to perform. The heated debates, the thoughtful discussions, the lengthy review of information, all evident in the panels, commissions, and councils formed to deliberate these matters, reflect society's genuine—desperately genuine—desire to make the right decisions.

Science cannot fail again to provide clear, accurate terminology to describe what eggs are asked to do. Eggs are now being asked not only to provide new members of the species, but also to provide tools to repair existing members of the species. Once the distinctions between these two tasks are made clear to society, the right decisions can be reached.

V. TERMINOLOGY

A. *Eggs Fertilized by Sperm*

For most of the centuries after the advent of the microscope in the mid-1600s, the term "embryo" was applied to that period of early development before the conceptus took on the appearance of its species. For the human, this is sometime after implantation and before all the organs appear. Human medical embryology texts still refer to the first two weeks after fertilization as the "ovum" period. Therefore, strictly speaking, the term "embryo" defines the human conceptus during the rapid growth period after implantation, when the embryonic disk has become distinct from trophoblast.

Accordingly, applying the term embryo to any stage of development before the inner cell mass forms is inaccurate. It is well known that blastocyst formation occurs without the concomitant formation of an inner cell mass, in which case embryonic development ceases. This line of reasoning points out the inaccuracies of both of the terms, "pre-implantation" embryo and "pre-embryo," which are applied to the stages of development that precede the hatched blastocyst stage, either in vitro or in utero. These terms clarified a stage of development for scientists but did little to enlighten the general public.

"Zygote" is a term that has been widely used to designate development before the blastocyst stage. Zygotic gene activation ("ZGA") is common scientific parlance to describe proteins that are expressed from the genes brought in by sperm and maternal genes that were not expressed in the egg. Strictly speaking, however, a zygote is defined as the pronuclear stage that appears following fertilization. This definition is strictly adhered to in the Australian Acts. Still, the term "zygote" clarifies that the early stages are not yet embryos.

The review of existing laws, codes and guidelines points out that "embryo" has become thoroughly ensconced in society's attempt to discuss, define, and understand early human development around the world. It may be futile to attempt to replace "embryo" with another more accurate term with respect to human eggs fertilized by sperm. The hope in this regard is to educate the public that a cleaving egg is not the same stage of "embryo" as an "embryo" two weeks following implantation in the uterus. A clear understanding that union of sperm and egg does not automatically form an embryo, that an embryo naturally arises from such a

form an embryo, that an embryo naturally arises from such a union in stages, each necessarily following the previous, which had to be completed with few or no flaws. Failure to accurately complete each step in sequence signals failed conception. The appearance of an inner cell mass is a minimal requirement for embryo status. Implantation and the development of an embryonic disk is a more accurate requirement for embryo status.

B. *Parthenogenesis*

An egg activated without sperm does not go through a zygote stage, which by definition is the union of sperm and egg. Since egg activation occurs spontaneously in the human ovary, and a parthenote baby has never been reported, the simplest explanation is that human parthenotes cannot develop to term. There is, therefore, no reason that parthenotes should be referred to as embryos.

Not all scientists will agree with this because the early cleavage stages appear identical to early stages that follow fertilization of the egg by sperm. Moreover, because of the chromosomal crossing-over that occurs during egg maturation,[145] the parthenote is not a clone of the woman even though all of its chromosomes are from her.

These considerations support the concept that clarity of language is best served by referring to parthenotes at all stages as just that, parthenotes, not embryos. "Two-cell parthenotes," "morula-stage parthenotes," and "blastocyst-stage parthenotes" are terms that accurately describe the cleavage stage attained by the activated egg. Since there is no reason to transfer a parthenote to a uterus, there is no need for a term that describes implantation by parthenotes.

Although parthenotes deserve the respect afforded a cell as precious as an egg, they are not embryos and therefore debates about moral, ethical, or legal status should not apply.

C. *Nuclear Transplants*

Nuclear transplant technology requires the most careful consideration with respect to accurate terminology.[146]

First, a name for an egg with no chromosomes is needed. "Cytoplast"

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[145] *See supra* Part II.A.

[146] A note of clarity needs to be added here with respect to the term "asexual reproduction" which appeared in the reports from both President Clinton's National Bioethics Advisory Commission and President Bush's Council on Bioethics. BIENNIAL REP., *supra* note 119; HUMAN CLONING AND HUMAN DIGNITY, *supra* note 75. The term should not be applied to nuclear transplants involving eggs. Eggs are obviously a sexual cell, and nuclear transplant cloning procedures require de-differentiation of the transplanted nucleus. For clarity of language, "asexual reproduction" should remain reserved for those processes which do not involve any gametes, nor any dedifferentiation, such as budding yeast.

is commonly used, but bears little specificity to its derivation from an egg. "Enucleated egg" has also been used, but lacks accuracy since the egg's chromosomes, not its nucleus, were removed. Several nuclear components, including the nuclear membrane, remain behind in the egg's cytoplasm. Some consideration needs to be given to the actual status of an egg with no chromosomes. Is it alive? It is a sphere of egg organelles,[147] enzymes, structural proteins, and nutrient stockpiles, collectively referred to as "ooplasm"; but without genes, it is not a cell. More accurate terms would be "ooplast," or "ovaplast."

The second is a name for the result of transplanting a new nucleus into the ovaplast. In fact, two names may be needed because the process of adding a new nucleus to the ovaplast sometimes involves not just transplanting the nucleus, but fusion with the entire cell, which includes both its nucleus and cytoplasm.[148] Distinguishing between cellular transplantation and nuclear transplantation may prove to be more biologically relevant than now appreciated because transplantation of the entire cell includes its sub cellular organelles, which creates a reconstructed "egg" cell that is a chimera of two sets of sub cellular organelles, which may prove to be physiologically significant.[149] Thus, nuclear transplants are somewhat different from fused cells.

Scientists and society have been struggling with a term for this type of genetically reconstructed egg. Because no term has become as entrenched as has "embryo" for a fertilized egg, there is opportunity to develop accurate technology. Since a single nucleus is transplanted into the egg, cloning is an accurate term for the process, but the word "clone" has come to mean the creation of an offspring genetically identical to an adult. The term is also loaded with the spectre of eugenics and genetically engineered individuals.

Several lines of reasoning argue against calling such a somatic-cell-ovaplast-construct an "embryo." First, by definition, they do not go through a zygote stage because they are not fertilized by sperm and the transplanted nucleus undergoes remodeling to a single, large pronucleus, reminiscent of the parthenote.

Second, they would only become embryos in the classical sense if they are transferred to the uterus and initiate implantation. At this stage they could rightfully be termed "embryos." Since the derivation of pluripotent stem cells will be the goal for human somatic-cell-ovaplast-constructs, they

[147] Cells contain small structures that are membrane-enclosed enzymes with specific functions, such as degrading bacteria, that are termed "organelles."

[148] The area of a cell between the nucleus and the outer membrane is the cytoplasm; it contains the enzymes and nutrients needed for cell function and communication with other cells, as well as organelles such as the mitochondria which generate the cell's energy.

[149] Jason A. Barritt, *Mitochondria in Human Offspring Derived from Ooplasmic Transplantation*, 16 HUM. REPROD. 513, 513 (2001).

will never achieve "embryo" status.

Somatic-cell-ovaplast-constructs undergo cleavage and development to the blastocyst stage morphologically similar to zygotes and parthenotes, which is the stage at which pluripotent stem cells could be isolated. The problem is what to call the cleaving stages between nuclear transplant and blastocyst. "Ovasome" is a term that was proposed[150] because it depicted the process of transferring a somatic cell into an egg with the purpose of creating more somatic cells and not offspring. The term was criticized in the popular press as being an attempt to side-step the potential for an egg-somatic cell reconstruct to become a cloned human. The term may not be the best, but it is a step in the right direction.

D. *The Future of Human Pluripotent Stem Cells Derived from Eggs*

1. *Parthenotes*

Although no pluripotent stem cell lines have been reported from human parthenotes as of this writing, current scientific evidence strongly supports success in this area within the near future. One promising possibility is that such human parthenote pluripotent stem cells ("hpPS" cells) could be derived from the eggs of pre-menopausal women with serious diseases, such as Type I diabetes or spinal cord injury. Once the technology is perfected to generate insulin-secreting cells, or spinal cord compatible neurons from hpPS cells, such women could be treated with cell lines derived from their own eggs. In many ways, this type of treatment is more closely related to autologous blood transfusion than to reproductive biology.

In addition, it seems highly likely that the efficiency of hpPS cell derivation may be improved by targeted manipulation of the egg's genetic information. Although not yet reported, an obvious example is insertion of a simple gene construct to encode a protein that better adapts the hpPS cells to laboratory culture conditions, or cryopreservation.

2. *Somatic-Cell-Ovaplast-Constructs (Ovasomes)*

Similarly, to ensure that constructs created specifically for the purpose of deriving pluripotent stem cells for therapy could not be diverted to attempts to clone a human, it may be possible to genetically engineer the nucleus to be flawed in a manner that favors the differentiation of the type of cell desired (e.g., an insulin-producing pancreatic cell), but as a consequence of the engineering has no hope of ever developing into a complete offspring under any circumstances. Although this specific experiment has not yet been reported, there is a large body of literature that

[150] Ann A. Kiessling, In the Stem Cell Debate, New Concepts Need New Words, 413 NATURE 453 (2001).

describes genetic manipulation of numerous animal species, especially mice. Such genetically manipulated animals have provided invaluable information about the physiologic roles of specific genes.

VI. SUMMARY AND CONCLUSIONS

We have an opportunity to potentially treat incurable diseases, estimated to afflict half of all Americans, by methods never before available. That opportunity is currently hampered by confusion with the perceived potential harm to society that would come from either sacrificing embryos or creating the technology to create cloned humans. Accurate terminology will alleviate some of the confusion so that appropriate, rather than theoretical, ethical issues can be addressed.

The terminology associated with fertilized human eggs may be so rigidly fixed by custom and case law that the extended use of "embryo" to encompass early cleaving egg stages may have to be accepted. If so, major efforts need to be undertaken to inform policy makers that nature has checks and balances in place to ensure that fertilized eggs acquire the true status of embryo only through the completion of defined developmental tasks. Whether or not society decides to support research on fertilized human eggs is a separate matter, to be decided by open public debate.

The terminology associated with parthenotes and somatic-cell-ovaplast-constructs has not yet been fixed by convention, and the opportunity exists to ensure that accurate language is consistently used to describe the relevant biology. This author proposes that routinely adopting the term "parthenote" for activated eggs with their own chromosomes is a simple, accurate solution to the description of deriving pluripotent stem cells from parthenogenically activated eggs. This author has further proposed a totally new term, "ovasome" to be applied to the creation of somatic-cell-ovaplast-constructs solely for the purpose of deriving pluripotent stem cells. Other terms may be preferred. Unless they are transferred to a uterus, they will not, in any event, become human embryos.