
Santa Clara High Technology Law Journal

Volume 19 | Issue 2 Article 5

January 2003

# The Ethics of Reproductive Cloning

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# SYMPOSIUM REVIEW

# THE ETHICS OF REPRODUCTIVE CLONING

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## I. INTRODUCTION

Reproductive cloning is unethical in its current technological stage. Understanding the important genetic and biological differences between an embryo produced by natural or assisted reproduction methods—such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI)—versus an embryo produced by reproductive cloning is essential in arriving at this position. A number of biological processes, necessary for the development of a healthy individual and the maintenance of a robust gene pool, are bypassed by the reproductive cloning process. From a medical ethics perspective, bypassing these processes subjects the cloned individual (and its future generations) to unacceptable levels of risk. From a societal perspective, the virtue of the ends of reproductive cloning must be

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The author wishes to thank Jonathan Saunders for thoughtful review and helpful suggestions, Martha Minion for research support and Monique Walton for help in preparing the manuscript for publication.

considered in light of biological urges, the influence of laws, and societal mores.

The ethical concerns of reproductive cloning received substantial attention following the cloning of Dolly the sheep in 1997, and were revived by recent Clonaid's recent claim that it had successfully cloned a human.[1] Even though there has been considerable sensationalism and hype surrounding these reports, the popular press must be credited for at least attempting to educate the general public on the underlying science of cloning technology, especially regarding the differences between therapeutic cloning and reproductive cloning.[2]

To be clear on terminology, the following discussion uses the terms "ethics," "cloning," and "reproductive cloning" in following manner:

- Ethics is a branch of philosophy dealing with what is good and bad and with moral duty and obligation.[3] It is a system of moral principles.[4] The argument presented below addresses both the medical ethics and broader societal ethics of reproductive cloning.

- Cloning is a term describing a process of producing copies of a cell, tissue, or organism from a single cell by mitosis, the asexually producing progeny of an individual.[5] In the research laboratory, cloning is frequently used to generate large quantities of genetic material for a wide variety of experimental applications, including research to identify disease-causing genes.

- Reproductive cloning is the process by which an embryo is produced through the removal and transfer of nuclear material in a cell, and the use of a growth medium to manipulate that cell into undergoing mitosis.[6] This process is the culmination

1. Associated Press, *Baby Said To Be Human Clone Goes Home From Hospital*, Dec. 31, 2002, *at* http://www.hannibal.net/stories/010103/new_0101030008.shtml.

2. *See* Gia Kolata, *The Promise of Therapeutic Cloning*, N.Y. TIMES, Jan. 5, 2003, at 7.

3. WEBSTER'S NINTH NEW COLLEGIATE DICTIONARY 426 (9th ed. 1983).

4. *See id.*

5. *See id.*, at 250; *see also* RANDOM HOUSE UNABRIDGED DICTIONARY (2d ed. 1993).

6. James McGrath & Davor Solter, *Nuclear Transplantation in the Mouse Embryo by Microsurgery and Cell Fusion*, SCIENCE, June 17, 1983, at 1300–02.

of advancements in recombinant DNA technology and IVF methods.[7] Reproductive cloning has been successfully employed in the lab to produce tadpoles,[8] frogs,[9] mice,[10] cows,[11] and sheep.[12]

For a number of fundamental biological reasons, reproductive cloning does not produce an identical copy of an individual. Genetically, reproductive cloning differs from procreation in that the nuclear genomes of two individuals are not combined in the same way; genetic recombination during this process occurs in a manner that does not result in a genetically unique individual. This technical and biological difference makes reproductive cloning significantly different than assisted reproduction methods, e.g., IVF and ICSI, even though both procedures require substantial human intervention.

## II. A BRIEF HISTORY OF REPRODUCTIVE CLONING

The history of the laboratory work leading to the reproductive cloning of mammals has been well-documented.[13] Briefly, in the 1960's John Gurdon combined an egg cell (complete with cytoplasm) from which the nucleus had been removed, with the nucleus of an intestine cell to clone frogs. [14] Donor-cytoplasmic material was not transferred however, and the resulting tadpoles did not survive to maturity.[15]

Fifteen years later, Solter and McGrath performed nuclear transfer to produce the first cloned mouse.[16] They changed Gurdon's method by fusing a mouse zygote acceptor cell, whose cytoplasm remained intact but from which the nucleus had been removed, with

7. John B. Gurdon, *Transplanted Nuclei and Cell Differentiation*, SCI. AM., Dec. 1968, at 24–35.

8. Clifford Grobstein, *External Human Fertilization*, SCI. AM., June 1979, at 57–67.

9. John B. Gurdon & Uehlinger V, *"Fertile" Intestine Nuclei*, NATURE, June 1966, at 1240–41.

10. McGrath & Solter, *supra* note 6.

11. Michelle Sims & N.L First, 90 PNAS USA 6143–47 (1993).

12. Ian Wilmut & Anelika E. Schneike et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, NATURE, Feb. 1997, at 810–13.

13. LEON R. KASS & JAMES Q. WILSON, THE ETHICS OF HUMAN CLONING, (AEI, 1998). *See also* Gurdon, *supra* note 9; Grobstein, *supra* note 8; Gurdon, *supra* note 7; McGrath & Solter, *supra* note 6; and Michelle Sims & N.L First, *supra* note 11.

14. *See* LEE M. SILVER, REMAKING EDEN: CLONING AND BEYOND IN A BRAVE NEW WORLD (Avon, 1997). *See also* Gurdon, *supra* note 9.

15. *See* Gurdon, *supra* note 7

16. *See* McGrath & Solter, *supra* note 6.

the donor nucleus from a genetically distinct mouse embryo.[17] Ninety-six percent of their embryos survived to the blastocyst stage, 16 % developed to term (compared to 15% of control animals), 11% survived to adulthood (compared to 10% of the controls), and half of the clones were fertile adults (compared to all 3 control animals).[18] The number of mature surviving animals in these experiments was ultimately small, due to the large number of embryos that did not survive to term in both control and experimental sets.[19] At the time, it was thought that the donor-cytoplasmic contribution led to the successful outcome of clones that developed into adult mice.[20]

In 1994, Michelle Sims and Neal First used embryonic tissue to clone a cow.[21] This accomplishment did not receive wide publicity similar to the cloning of Dolly however, largely because Sims used embryonic tissue. Although it was a significant achievement, the use of embryonic tissue to produce this clone tempered enthusiasm for the technology in general. It also triggered ethical concerns of where this practice might lead, should cloning enter the realm of contemplated human reproductive therapies.

The cloning of Dolly in 1997 aroused tremendous interest because for the first time an adult donor cell had been used to produce a cloned mammal. This was significant since it presented the opportunity to clone without using an embryonic donor cell. Dolly was cloned using somatic cell nuclear transfer, a procedure by which the nucleus containing genetic material is removed from an unfertilized egg, then replaced with genetic material from the adult cell to be cloned.[22]

In his experiments, Ian Wilmut performed 276 nuclear transfers, implanted embryos in 13 ewes, and obtained one pregnant sheep that went to term and produced Dolly.[23] It is a delicate procedure. The age and integrity of the transferred DNA is critical and the medical implications for the cloned sheep are still being explored. In Dolly's case, she experienced some age related diseases such as arthritis earlier than she would have in normal life, eventually developed lung disease, and had to be euthanized.[24] Whether this was an artifact of

17. *Id.*
18. *Id.*
19. *Id.*
20. *Id.*
21. *See* Michelle Sims & N.L First, *supra* note 11.
22. *See* Wilmut & Schneike et al., *supra* note 12.
23. *Id.*
24. Reuters, *Mystery Over Death of Australia's 1st Cloned Sheep*, (Feb. 7, 2003),

her environment or a ramification of being cloned remains to be determined. Nevertheless, the lesson to garner is that adapting methods used to clone frogs, mice, and sheep to the reproductive cloning of humans raises many important ethical questions.

## III. THE MEDICAL ETHICS OF REPRODUCTIVE CLONING: WHAT IS (UN)KNOWN

It is medically unethical to perform reproductive cloning on humans at the current state of technology. The contribution of all biological and developmental components to the successful genesis of a healthy human is not understood, and thus determining the amount of acceptable risk is not yet possible. All procreated mammalian embryos undergo genetic recombination and a process called genomic imprinting.[25] This still somewhat mysterious process results in the differential expression of a gene, driven by which parent contributed the gene.[26] Genomic imprinting is a mammalian-specific form of gene regulation in which one of the two parental alleles is preferentially expressed over the other.[27] The imprint is passed on from the parent to the offspring and then erased and reset in the germ line cells of the offspring to reflect the sex of the parent from whom the alleles were inherited in the fertilized egg.[28] Thus, the parental origin of the chromosome appears to be relevant in this process.[29] In the embryo resulting from reproductive cloning, the genome is not a genetically recombined genome from two individuals.

How, or if, the genomic imprint passed along from the adult cell affects the health of the clone is unknown. Data suggests that the lack of genetic recombination in cloned complex organisms is problematic and may adversely affect genomic imprinted genes.[30] Humphreys et al., found that the gene activity of hundreds of genes which are normally imprinted in the procreated mouse are abnormally expressed

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*available at* http://news.awse.com/10-Feb-2003/Technology/17555.htm.

25. Carmen Sapienza, *Parental Imprinting of Genes*, SCI. AM., Oct. 1990, at 52–60.

26. Judith G. Hall, *Genomic Imprinting: Review and Relevance to Human Disease*, AM. J. HUM. GENET., May 1990, at 857–873. *See also* T. Moore & D. Haig, *Genomic Imprinting in Mammalian Development: A Parental Tug of War*, TRENDS IN GENET., (Feb. 1991, at 45–49.

27. *See* Sapienza, *supra* note 25.

28. *See* Kolata, *supra* note 2

29. *See* Sapienza, *supra* note 25.

30. David Humphreys et al., 99 PNAS USA 20, 12889–94, TELECHEM INTERNATION INC. (2002), *at* http://arrayit.com/e library/h/HumpherysD2002/humpherysd2002.html.

in the cloned mouse.[31] Four percent of the 10,000 genes surveyed were abnormally expressed and approximately half of those genes are known to be imprinted genes.[32] Genomic imprinting abnormalities and disorders of imprinted genes result in syndromes or symptoms in which there is abnormal tissue or organ growth, such as Prader Willi Syndrome[33] and Angelman Syndrome.[34] Such disorders arise from imprinting malfunction and *uniparental disomy*, a state arising when chromosomes donated by egg and sperm incorrectly segregate, presenting the embryo with two copies of a chromosome from one parent or the other, rather than from both.[35] The mechanism of genomic imprinting is not completely understood and there is a considerable lack of knowledge regarding the impact reproductive cloning has on this process.

Not all genetic material is in the nucleus; DNA is also found in the mitochondrial structure. In reproductive cloning, the nuclear genome is transferred to the donor cell without consideration of the state of the mitochondrial genome;[36] nuclear transfer is only concerned with the combination of nuclear cytoplasm from both the donor and acceptor cells.[37] Though one would anticipate that clones would contain mitochondrial DNA from both acceptor and donor cells, in a study evaluating mitochondrial DNA in Dolly and ten other nuclear transfer-derived sheep, Mathew Evans reported that mitochondrial DNA came solely from the recipient enucleated egg cells; no donor mitochondrial DNA was detected.[38] In other words, Dolly (and the other sheep studied) was not a perfect genetic replicate of the sheep Wilmut was attempting to clone. The effect this result

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31. *Id.*

32. *Id.*

33. Robert D. Nicholls & Joan H. Knoll et al., *Genetic Imprinting Suggested By Maternal Heterodisomy in Non-Deletion Prader-Willi Syndrome*, NATURE, Nov. 16, 1989, at 281–85.

34. Joan H. Knoll & Robert D. Nicholls et al., *Angelman and Prader-Willi Syndromes Share a Common Chromosome 15 Deletion But Differ in Parental Origin of the Deletion*, AM. J. MED.GENET., Feb. 1989, at 285–90; Charles A. Williams & Roberto T. Zori et al., *Maternal Origin of 15q11-13 Deletions in Angelman Syndrome Suggests a Role for Genomic Imprinting*, AM. J. MED. GENET., Mar. 1990, at 350–53; Joan H. Knoll & Cheng S.D. et al., *Allele Specificity of DNA Replication Timing in the Angelman/Prader-Willi Syndrome Imprinted Chromosomal Region*, NAT. GENET., Jan. 1994, at 41–46.

35. Jill Furnival and Wendy Robinson, *Uniparental Disomoy*, CHROMOSOMAL MOSAICISM, *at* http://www.medgen.ubc.ca/wrobinson/mosaic/upd.htm (last modified Apr. 18, 2001).

36. McGrath & Solter, *supra* note 6.

37. *Id.*

38. Matthew J. Evans et al, *Mitochondrial DNA Genotypes in Nuclear Transfer-Derived Cloned Sheep*, NATURE GENET., Sep. 1999, at 90–93.

has on the health and life span of the clone has yet to be identified.

DNA collects changes (or polymorphisms) overtime, and some of these changes may occur in regions that affect the health of the organism.[39] This accumulation of mutations is part of the aging process in all plants and animals.[40] DNA repair mechanisms are not perfect and, as an organism ages, variations and mutations are collected in its DNA.[41] The ends of chromosomes (the telomeres) also shorten as a person ages,[42] exhibiting the correlation between chromosome length and life expectancy.[43] The medical effect of a child carrying "old" chromosomes is currently unknown. The data is conflicting on how reproductive cloning affects telomere length.[44] In Dolly, the telomeres reflected the age of the DNA donor.[45] However, another study by Lanza et al., found that the telomeres were regenerated in cloned cows and no longer reflected the age of the DNA used for the nuclear transfer.[46] The important point is that the impact of carrying aged chromosomes or the mechanism by which telomeres may be regenerating in some cloned mammals and not in others is simply not known. What is known is that only 1–5% of cloned animals survive to adulthood.[47]

It is also known that environment plays a role in shaping an individual's health and well being. Even though "identical" twins share the same DNA, they are not identical since the effects of their environment are ultimately manifested in nuanced ways. It is not known precisely why they differ, although there are some clues. [48] For instance, environment affects development; even the intrauterine environment has myriad affects on the developing fetus and

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39. LUBERT STRYER, BIOCHEMISTRY 597–99, 635-39 (W.H. Freeman and Co., 2d ed. 1981).

40. Robert E. Ricklefs and Caleb E. Finch, *Patterns of Aging*, Aging: A Natural History, 1995, *available at* http://www.usc.edu/dept/pubrel/trojan-family/spring02/Aging/Patterns.html.

41. *See* BIOCHEMISTRY, *supra* note 39

42. Broccoli D. and Cooke H. *Aging, Healing, And The Metabolism Of Telomeres.* AM. J. HUM. GENET., Apr. 1993, at 657–60.

43. D.A. Banks & M. Fossel, *Telomeres, Cancer, and Aging. Altering the Human Life Span*, JAMA, Oct. 22-29 1997, at 1345–48.

44. Robert P. Lanza & Jose B. Cibelli et al., *Extension of Cell Life-Span and Telomere Length in Animals Cloned from Senescent Somatic Cells*, SCIENCE, Apr. 28, 2000, at 665–69.

45. *See* Banks and Fossel, *supra* note 43.

46. *See* Lanza and Cibellti et al., *supra* note 44.

47. *See* THE ETHICS OF HUMAN CLONING, *supra* note 13; David Humphreys et al., *supra* note 30, 99 PNAS USA at 12889–94.

48. Andrew K. Hotchkiss & Joseph S. Ostby et al., *Androgens and Environmental Antiandrogens Affect Reproductive Development and Play Behavior in the Sprague-Dawley Rat*, ENVIRON. HEALTH PERSP., Jun. 2002, at Suppl. 3:435–39.

subsequent disease susceptibility and fertility in adults.[49]

There is so little information correlating variation in nuclear and mitochondrial genomes, environment, developmental processes, and laboratory technique and successful outcome that it is difficult to draw any conclusion other than that it is medically unethical to subject a child to the risks of reproductive cloning.

## IV. SOCIETAL ETHICS OF REPRODUCTIVE CLONING: WHAT IS (UN)KNOWN

Some day many more of the complexities, nuances, and interactions involved in the growth and development of a healthy human individual will be understood. Taking into consideration the definition of ethics,[50] and assuming that all of the medical and technical questions could some day be addressed, is reproductive cloning unethical from a societal perspective?

The motives and ends of reproductive cloning merit examination. The most likely motive for reproductive cloning is the desire to possess a baby. This is a good and simple motive and certainly an understandable basic human drive. People unable to conceive naturally, or via fertility drugs or assisted reproduction, may consider reproductive cloning as just another reproductive option. But is it really just "another form" of assisted reproduction? Notwithstanding the fact that cloning does not address the broad spectrum of problems associated with embryo implantation and carrying a pregnancy to term, there is a complete lack of evidence supporting the notion that reproductive cloning would be any more successful in producing a healthy full-term baby for couples who have been unsuccessful with IVF or ICSI. There is also one important distinction that highlights to fundamental disparity between reproductive cloning and assisted reproduction methods, namely that all methods other than reproductive cloning generally allow for genetic recombination and subsequent normal genomic imprinting, whereas cloning is nearly one-hundred percent artificially cultured.

What about "the moral dut[ies] and obligation[s]"of such

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49. Paola Palanza & Sara Morley-Fletcher et al., *Novelty Seeking in Periadolescent Mice: Sex Differences and Influence of Intrauterine Position*, PHYSIOL. BEHAV., Jan. 2001, at 255–62. *See also* Delphine Jaquet & David A. Tregouet et al., *cFLIP Protein Prevents Tumor Necrosis Factor-Alpha-Medicatd Induction of Caspase-8-Dependent Apoptosis in Insulin-Secreting BetaTc-Tet Cells*, DIABETES, Jun. 2002, at 3473–78.

50. The values relating to human conduct, and actions, what is good and bad, and with moral duty and obligation. *See* WEBSTERS, *supra* note 3.

actions?[51] That which can be achieved experimentally may not be desirable for society. Decisions and choices are made within the framework of what is known and understood: biological urges, the influence of laws and societal mores, and of course limited resources. People make individual choices everyday that affect air and water quality and conservation of the earth's resources; one of these choices is the creation of a family. Just as everyone shares, in an individual way, the responsibility to conserve water, energy, and the earth's resources, everyone also shares the responsibility to sustain a healthy gene pool. Elimination of the process of genetic recombination from the process of reproduction removes the natural mechanism that sustains a healthy and diverse gene pool, putting us on the slippery slope of eugenics and designer babies.

## V. CONCLUSION

Ultimately, this discussion is about an individual, a child, produced by reproductive cloning, thus the welfare of children is an important component of this argument. There are currently millions of healthy, eager children in welfare institutes and orphanages waiting to be adopted.[52] There are only about 15,000 international adoptions in the US every year and about double that number worldwide.[53] Furthermore, there are 450,000 children in foster care in the U.S. alone, 100,000 of which will be unable to return to their biological families and are awaiting loving new homes.[54] Unfortunately for most, it will never happen. The effort to recycle has been more successful for cans and bottles than for children. Millions of children are waiting to be given a chance to have the family experience that so many take for granted.

Changes in attitudes and laws surrounding adoption and the adopted are needed. Why not teach about adoption as a reproductive choice in high school reproduction/sex education classes? We need to educate young adults about the alternatives to natural conception and artificial methods, and raise their awareness regarding the dearth of homes for the millions of children in welfare institutes worldwide. Domestic laws should be modified to make it easier for stable, competent, economically-secure adults to adopt (irrespective of

51. *Id.*

52. *See e.g.,* National Adoption Information Clearinghouse, *at* http://www.calib.com/naic/.

53. *Id.*

54. *See* HILLARY R. CLINTON, IT TAKES A VILLAGE (Simon and Schuster, 1996).

sexual orientation). Our government should be encouraged to work with international organizations toward expediting the currently slow, onerous, and exclusive cross-border adoption process. Finally, for the time being our government must encourage making choices to spend medical research dollars on the treatment and cure of diseases before the reproductive cloning of humans.