Analysis (Perspective)

Human Cloning: Who's Concern?

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SUMMARY

Cloning is basically a biological mechanism in which parthenogenetic reproduction employed by one or more genetically identical cells, plants or organisms are derived from one parent. The word clone is from the Greek word "klon", meaning a twig or slip from a plant. By taking many cuttings from one parent plant, genetic replicas with identical features and functions can be developed. The recent successful cloning from an adult sheep cell has raised the possibility of using asexual means to replicate humans. Through cloning the following clinical questions might be resolved: the course of spontaneous abortions, embryogenesis, carcinogenesis, and the use of embryonic tissue for transplantation. However, reproducing humans by use of cloning has raises serious legal, religious, and social problems. There are two methods used for cloning humans namely nuclear cloning and embryo splitting. Nuclear cloning in human reproduction should be prohibited because there are no extra major benefits by its application. It can only create additional medical, ethical, and social problems. The potential of cloning by embryo splitting for minimizing clinical costs and risks as well as increasing the rate of success for couples who are infertile and having children for them is a challenge. The minor legal and religious problems can finally be settled. If policymaker's guidelines win international acceptance and if they succeed, it may take less time to reach this goal.■

KEYWORDS Clone; Human being; Medicine; Ethnicity; Reproduction

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Cloning is basically a biological mechanism in which parthenogenetic reproduction is employed by which one or more genetically identical cells, plants or organisms are derived from one parent (1). The word clone is from the Greek word klon, meaning a twig or slip from a plant. By taking many cuttings from one parent plant, genetic replicas with identical features and functions can be developed. Reproduction by cloning is broadly used in plants and in the biological industry. Today biotechnology routinely uses recombinant vectors and eukariotic or bacterial cells as hosts for replication of specific DNA fragments from highly selected DNA molecules. Although cloning in plants and certain species of amphibians and viruses is the physiological way of reproduction, in mammals it is naturally impossible. In 1997, Wilmut and colleagues took a mammary cell from an adult sheep and cloned it. He developed this cell and grew a sheep embryo to term. This achievement of Wilmut et al. again raised this method of reproduction to medical and social criticisms (2). The potential benefits of this technology in mammal reproduction versus the possible mutation risks of the cloned products, the implication of genetic imprinting, and DNA methylation during cell cloning are the main issues of concern.

TYPES OF CLONING

Cloning presents a genetic control of mammalian cell reformation and development (3). In the strict sense of the word, it is using an adult cell so that an exact replica of the adult single parent is produced. There are two possible approaches for successful cloning: first, the method of nuclear transfer, by which the cloned products are genetically identical to their uniparental source; and second, the method of embryo splitting, by which all cloned products have identical genomes but different from their biparental origin.

CLONING BY NUCLEAR TRANSFER

By this method of cloning a retrieved nucleus is transferred in a recipient mature oocyte of a similar species which has been previously enucleated (4, 5). The donated nucleus can be from an adult or an embryonic cell or a cell from a cell line, and the recipient cell can be a somatic or a germinal cell.

Gurdon, in 1968, constructed clones by using nuclei from intestinal cells of frog (somatic cells) and frog oocytes with then (6). From a single source he succeeded in producing many offspring but the majority of these clones were malformed. He showed that the genetic information in nuclei from many cells can reform into a new frog whose genetic makeup and appearance was identical to the nuclear donor. An enucleated oocyte was used as a recipient to provide the necessary milieu for growth. Mammals have proven more difficult to clone. Illmensee and Hoppe, in 1981, showed that cloned mouse embryos were difficult to grow (7). On the contrary, sheep or cattle embryos, individual nuclei, or blastomeres in the 16- to 32-cell stage remain relatively undifferentiated and that's why can be employed in nuclear transfers (5). In 1986 Willadsen described cloning in sheep by nuclear transplantation (4). This was followed by reports of cloning in cattle, cloned embryos up to the 64-cell stage (5), and cloning in rabbits (8). Bovine embryos also develop normally in surrogate sheep and rabbits. Campbell et al., in 1996, cloned lambs by nuclear transfer (9). Lamb embryos were cultured and permanent cell lines were established. Lamb enucleated oocytes were then fused with a single cell from the totipotent cell line. The formed embryos were transferred temporarily to recipient ewes and their development was evaluated after 7 days. The successful morullae and blastocysts were then transferred to surrogate ewes and allowed to develop to term. Of 277 adult cells fused with ova, only 13 pregnancies resulted and only 1 ewe was born alive (2).

The Technique of Cloning By Nuclear Transfer

Micromanipulation. The zona pellucida of the recipient oocyte is slit and the nucleus is aspirated and transferred with a micropipette into another cell, which is primarily enucleated (10).

Fusion of the donor blastomere and recipient oocyte is achieved by an electrical current (electroporation/ electrofusion) (11). Conditions to optimize fusion need to be determined individually. Sufficient contact between relevant cell membranes, a nonelectrolyte fusion medium, and proper alignment of cells seem to be critical factors for successful fusion (12). After nuclear transfer and fusion, cloned embryos are left in culture (animals, 5-6 days; human, 24-48 hr) to recover and develop. At this stage, cloned embryos that develop normally can be used for further nuclear cloning and transfer, thereby increasing the number of potentially cloned animals. Compact morulae and blastocysts recovered from animal oviducts or in vitro incubators are then transferred to surrogate mothers for full development to term. In vitro culture systems are quite efficient (3). Most of the cloned embryos are lost during the recovery stage. It is expected that, with time, experience will be gained and animal cloning by nuclear transfer will become more efficient.

Biological Events During Cloning by Nuclear Transfer

The development of embryos produced by nuclear cloning depends on the maintenance of normal ploidy and the creation of the conditions for developmental regulation of gene expression. These are influenced by the donor and recipient cell interaction as well as by the donor cell cycle stage and recipient cell energy resources (13). In mammals most of the donor nuclei used was in either the S or the G2 (nondiploid) phase of the cell cycle (14). The preferred recipient oocyte stage is metaphase II at diploid arrest. When nuclei in S or G2 are introduced into metaphase ll-arrested oocytes, they tend to undergo additional DNA replication and premature chromosomal condensation, resulting in abnormal

development (15, 16). Theoretically, when the recipient cytoplasm is prepared by enucleation of an oocyte at metaphase II, the risk of chromosomal damage is less, while normal ploidy is maintained by transferring a diploid nucleus (17). There is an advantage of cells providing the transfered nuclei when they are in the G0 or G1 phase of the cell cycle. Quiescent diploid donor cells (also known as G0) can be produced by decreasing serum concentration of the medium from 10% to 0.5% for 5 days, causing the cells arrest in G0 (exiting the growth cycle), thus giving a better chance for synchronized reprogramming (9, 14, 18). Further experiments are required to define the optimum cell cycle stage for nuclear transfer. The cytoplasm of an enucleated oocyte provides the appropriate milieu for the donated blastomere to develop as well as specific factors for reprogramming the transplanted nucleus. The recipient oocyte does not have to be from the same animal to be cloned but success is more likely if it comes from the same species. When oocytes are used as the recipients instead of other cells, the chance for normal development is far better. This suggests that cytoplasmic factors found in the recipient oocyte trigger reprogramming of the transferred nucleus and gene expression. Ovulated oocytes are much better recipients than zygotes either due to the longer reprogramming period or because of the more suitable cytoplasm. In this context, identifying the cell cycle stages which enhance opportunities for reprogramming, nuclei from a wide range of cell types might prove to be totipotent. The overall live birth compared to the number of cloned embryos is currently very low. This is attributed to

- Accumulation of deleterious factors produced during enucleation and replacement of the nucleus;
- Incompatibility between the recipient cell and the donated nucleus;
- Bad synchronization of biological functions between the recipient cytoplasm and the donor nucleus, resulting in inadequate functional reprogramming of the donor nucleus;
- Probable partial loss of imprinting; and
- Limited energy resources of the recipient cytoplasm—the messenger RNAs and proteins stored in the oocytes can support mammalian development for only a short time (13).

Potential Genetic Risks during Cloning by Nuclear Transfer

The differentiation process of primitive germ cells into specific tissue types occurs early during development; it is different between species and depends on complex interactions within the gene itself; and with other genes, the environment, and different binding proteins. In cloning the sheep mammary cell there were no irreversible changes in the genetic. This is in line with the view that mammalian differentiation is generally achieved by systemic, changes (sequential) inexpression of genes are brought about by interactions between the changing cytoplasmic environment and the nucleus. Cytoplasmic factors necessary for chromosomal remodeling and genome activation are implicated in DNA replication after fertilization. By arresting donor nuclei in G0, better synchronization of DNA replication between the cytoplasm of the recipient oocyte andthe transplanted nucleus is expected. It is presumed that transcription factors and chromatin-binding proteins are increased. Once development is initiated under such conditions the incidence of chromosomal abnormalities is reduced. Nuclei in the early preimplantation stages are mainly in S or G2, and it is very difficult (if not impossible) to arrest embryonic stem cells in G0 by serum starvation (2, 19). In sheep transcription of the embryonic genome does not begin until the 8- to 16-cell stage, whereas in the mouse transcription occurs in the late 2-cell stage (20). Unsuccessful DNA replication synchronization might explain the failure to clone mice. If these aspects are significant, then reproducing the experiment in other animal species might be very difficult or impossible, as the onset of embryonic transcription varies between species. The magnitude of contribution of the corresponding genes in reproduction is also not well understood. Most genes are expressed by two alleles, one maternal and one paternal. Genes subjected to imprinting are molecularly marked before fertilization, thus at one of the parental alleles in the offspring, they are transcriptionally silenced (21). Imprinting of DNA normally occurs during gametogenesis. Modification in the DNA is indicated by reversibility of imprinting present, which is reversed if germ cells are produced in the next generation (22). Genomic imprinting has been implicated in the pathogenesis of inherited tumors, certain human diseases, and sporadic tumors (23). Some of these are myotonic dystrophy, Huntington's chorea, Wilms' tumor, hepatoblastoma, embryonal rhabdomyosarcoma, and neuroblastoma (22). However, the information about how genetic imprinting is implicated during cloning is still to be found. The status of methylation is another unclear issue because inactive genes tend to be more methylated than active ones. Methylation variations have been noted during embryogenesis and implantation. This was closely related to embryo chromosomal characteristics and development. In cancer both hypomethylation and hypermethylation have been reported. Studying methylation during and after animal cloning might lead us to certain important biological clues. Mutations are constantly occurring in DNA; the great majority is in the noncoding DNA and, so, appears to have no biological significance. DNA repair mechanisms enable mutations to be corrected. Mutations are the ultimate source of genetic variation. Mutations can have selective effects leading to balanced polymorphism in an evolutionary sense. Until balanced by the loss of homozygotes population, the gene frequency of heterozygous (advantageous) will increase. This evolutionary balanced polymorphism is lost by using nuclear cloning as the method of reproduction (3). The technique of arresting cells at the G0 phase by serum starvation seems to be very inaccurate, while the existence

of any potential negative effects on the progeny remains to be determined. The formation of totipotent cell lines from early embryos and the long quiescent period are other substantial risk factors for contamination, eventually leading to chromosomal aberrations. The need for enucleation of the recipient oocytes leads to the sacrifice of a lot of oocytes of the same or different species to be cloned.

CLONING BY "EMBRYO SPLITTING"

By this method embryo blastomeres are separated and left to grow, forming daughter embryos with the identical genotype and phenotype of the "mother embryo." This separation must be performed in early embryonic development, when blastomeres retain their potential to differentiate into all different cell types. Splitting these blastomeres and transferring them into the cell membrane of a previously enucleated cell gives rise to two, four, or more individuals according to the number of blastomeres. This number correlates with the number of undifferentiated cells and the embryo cleavage stage, which differs from species to species. An undifferentiated cell can give rise to all other cell types because of its potential to activate any gene or any chromosome. Although parthenogenesis in animals is not feasible in vivo, in 1952 Briggs and King took nuclei from amphibian frog embryos and developed them into multiple blastula-stage embryos. Those embryos grew a little more but all died at the tadpole stage (24).

The Technique of Embryo Splitting

At the early stage of embryo development, usually at the four- or eight-cell stage, a micropipette is used to aspirate each cell individually and place it in the cytoplasmic membrane of another previously enucleated mature cell or in an artificial membrane. This technique of embryo micromanipulation is widely used today for preimplantation diagnosis and is a relatively simple and quick operation after gaining experience. The separated blastomeres retain their totipotential and, as far as they do so, theoretically can divide and split indefinitely, producing individual cells of the same identical genetic trait. Therefore, using the current IVF technology, embryos can be obtained for preimplantation diagnosis, selecting the healthiest and the best in morphology for transfer. By this method donor embryo can be used fresh or frozen.

Experiments in Animals

Baker and Shea, in 1985, produced cloned twin cattle by embryo splitting (25). Wolf, in 1997 on the Internet, reported cloning by embryo splitting of nine embryos of rhesus monkeys. They were implanted in adult females and resulted in three pregnancies and two live births (26).

The Limitations of Cloning by Embryo Splitting

This method of cloning by embryo splitting is easier and less complicated than nuclear cloning, and it is effective to produce a large number of genetically identical offspring, however, not identical to their parents because they are of a biparental origin. Because of the biparental genomic contribution, the risk of unbalanced translocations is reduced but the selection potential of specific genetic traits is limited. Theoretically, once a donor embryo was identified, it would be possible to produce unlimited number of clones, because further nuclear transfers recycle embryos at the embryo culture stage. Cloning by embryo splitting achieves a relatively smaller number of clones, the selection of specific genetic traits is more difficult, and it is more time consuming than nuclear cloning. However, cloning by embryo splitting seems to be more successful as far as birth rate per number of clones (3).

CLONING IN HUMANS

The recent successful cloning from an adult sheep cell has raised the possibility of using asexual means to replicate humans. Through cloning the following clinical questions might be resolved: the course of spontaneous abortions, embryogenesis, carcinogenesis, and the use of embryonic tissue for transplantation. However, reproducing humans by use of cloning has raises serious legal, religious, and social problems. Nuclear cloning and transfer can potentially be applied for the following medical indications:

- Women with premature ovarian failure due to low oocyte availability or who do not wish to use donated oocytes.
- Couples carrying a recessive genetic disease or males or females with dominant genetic disease or
- Single women not interested in using donor sperm.
- Improvement of IVF results, especially in low responders who produce only small amount of oocytes-embryos.
- Sex preselection, e.g., in male hemophilic patients.
- Reduction of multiple pregnancies and, hence, the reduction of the risk for ovarian hyperstimulation syndrome and number of premature neonates in women with cystic ovaries by transferring only one embryo per cycle. The large numbers of cryopreserved embryos give extra reassurance of embryo availability.
- Using cloned embryos or organ donation.
- Study of cell growth and development in order to develop understanding of embryogenesis, senescence and carcinogenesis
- Ovulation induction and oocyte retrieval, which can be performed only once.

HUMAN CLONING BY NUCLEAR TRANSFER

Cloning by nuclear transfer is asexual reproduction and therefore can have evolutionary consequences and detrimental biological effects on the genome of humans, as well as ethical, social implications and legal. In the event of a triumphant human cloning, an indefinite cell line will be created This type of cloning can lead to the loss of naturally existing selective advantage that results from the organism's interaction with its environment. There is a possibility of mutations introduced to the human genetic pool and risk of an accumulation of deleterious recessive genes after several generations of nuclear transfer cloning, which may result in an increase in malformations and various diseases. Take the example of sickle-cell anemia and cystic fibrosis, today the genes for sickle-cell anemia and cystic fibrosis is present in a high frequency among the human population, but because of the fact that they are heterozygous, many mutations exist, resulting in a large variability in the degree of the disease (27). Bypassing these evolutionary processes by skipping the natural biological route may lead to the creation of organisms with lethal genes or morbid. Such genetic errors would also be reproduced within the germline, thereby ensuring transmission to progeny. It is unacceptable in clinical practice as it is the major biological limitation in human cloning. Human cloning by nuclear transfer raises another issue regarding the aging of the cloned individual. There are no data yet available in animal species.

HUMAN CLONING BY EMBRYO SPLITTING

The first experiment on human embryo cloning was reported at the annual meeting of and the Canadian Fertility and Andrology Society and the American Fertility Society in 1993. Seventeen polyspermic embryos consisting of a few cells each were further divided to form 48 blastomeres altogether. These blastomeres were then split, covered with an artificial coating membrane, and placed in culture. The single cell divided an average of three times before dying, while others survived to divide five times into 32-cell embryos (28). These results demonstrated that cloning in human embryos is feasible. The splitting of embryos by micromanipulation, usually into two blastomeres or more, creates two identical embryos. Each of the formed embryos can be split to produce more embryos, up to six to eight cleavage divisions, and theoretically this can be repeated indefinitely. The split embryos can be transferred to the uterus to develop and grow. This technique of splitting is already applied for the procedure of preimplantation diagnosis and for sex preselection. Nevertheless, after establishment of a diagnosis the blastomere is not used further. The application of cloning by embryo splitting involves a certain risk of embryo damage and destruction, but this may be overcome by the clinical advantage of the big number of "back-up" embryos. The data in the last decade show that, with each new applied technology in reproduction, including conventional IVF, cryopreservation, ICSI, and preimplantation diagnosis, the rate of gametes or embryo damage is steadily declining with experience. Therefore, manipulation of embryos and possible damage to them should not prevent further investigation of human cloning by embryo splitting. The concern that embryo splitting could result in the birth of identical cloned embryos several years apart should not discourage the application of this technique. This can be controlled by limiting the period of transfer of embryos to 5 years. Using the embryo splitting method may be dangerous for society because an unlimited number of clones can be reproduced. Therefore, the number of cloned embryos should be limited to two, and after their birth, with all respect to preembryos, the cryopreserved preembryos should be thawed. This resembles the natural birth of identical twins and should not raise any additional ethical questions The cloned identical "twins" (or more) may be effected be environmental conditions resulting in finally different personalities but they will carry the same genotype as the cloning is performed by nuclear transfer. By limiting the number of embryos transferred, the risk of abusing this technique is minimized. Reproduction of embryos with the same genome for commercial reasons or as a source of organ transplantation should be strictly prohibited. Using cloning in humans by embryo splitting carries no risk of creating a superman or genetic alterations, and the selection of elite individuals is biologically impossible because the cloned embryos are the product of both maternal and paternal gametes.

Clinical and Cost Benefits of Human Cloning by Embryo Splitting

Cloning by embryo splitting can offer the opportunity to a couple who needs IVF to perform ovulation induction and oocyte retrieval only once, and the embryos formed can be cloned, transferred, and cryopreserved accordingly. Such a management would excessively reduce costs and IVF complications. After two children the rest of the cryopreserved embryos should be destroyed. This is the most difficult stage of this procedure. Strict legal regulations must be formed to assure that no doctors or parents would overrule these regulations. Recently preimplantation biopsy and diagnosis have given additional information for the potential of this technique. The pregnancy rates were similar to those of intact embryo transfers after embryo manipulation for preimplantation diagnosis purposes (X-linked disorder) (29). This shows that human embryos at the early morula stage have totipotential characteristics and remain unaffected after delicate micromanipulation. This is also demonstrated by intracellular sperm injection in IVF. The possibility of conducting genetic analyses on developing embryos prior to implantation appears to be a natural extension of IVF and ET. The issue of sacrificing for genetic analysis a cell mass with the potential for normal embryo development will not be acceptable to some ethicists, however, today all the big IVF centers are allowed to perform preimplantation diagnosis on human embryos. Investigating the legal and ethical implications of new technologies is essential. The public

may welcome ways in which a government can have a check on cloning, but the needs nowadays are more ways that scientists and people can ethically fathom it.

Preimplantation Diagnosis as a Prerequisite of Cloning By Embryo Splitting

There are two main reasons to perform a routine preimplantation genetic diagnosis before cloning embryos, at least in the first attempts: (i) to rule out potential genetic abnormalities triggered by the cloning technique and (ii) to identify the affected embryos and to clone only the healthy ones. It is well-known that induction of ovulation produces embryos with more frequent chromosomal abnormalities than those in spontaneous ovulation; hence more abortions are evident in IVF patients. If both parents have a recessive disease, the chance of having affected embryos is 25%, and in the case of a dominant disorder, 50%. Hence it is important to identify the healthy embryos to be cloned. National committees should help to integrate preimplantation diagnosis in all IVF laboratories so more diseases can be diagnosed. Such a data bank would help later to establish the foundations and open the doors for human cloning. Proposals for human cloning must therefore be assessed carefully to ensure that they do not promote the development of adverse effects of the cloned embryos and that they constitute an appropriate use of resources. We believe that the first trials of human cloning by embryo splitting would be justified if they were performed on infertile couples with a high risk for genetic diseases. Choosing the healthy embryo to be cloned, then transferring it, remains as the single procedure to be repeated until the patient has a baby.

Religious Aspects of Cloning

The practice of reproduction is still under the influence of different religious doctrines. Christian churches, Islam, and Buddhism do not support it or are clearly against it. The Roman Catholic Church prohibits it because it is contrary to the moral law and in opposition to the dignity both of human procreation and of conjugal union. From Islam's view point human cloning separates the act of reproduction from marriage and human relationship Buddhist think that cloning will result in the problem of inheriting of karma. Karma is often conflict with reincarnation in Buddhism. The Jewish view is that it may be applied only in cases where there is a clear therapeutic indication. Therefore, religious attitudes should be taken into consideration before the application of cloning in humans.

Legal Aspects of Cloning

International ethical guidelines such as those of the American congress, FIGO, European council and WHO already support animal cloning. At present several countries such as the United Kingdom, Denmark, Germany, Belgium, The Netherlands, and Spain have prohibited human cloning by legislation. In several countries it is forbidden by regulations. Human cloning is prohibited by The Human Fertilization and Embryology Act of 2008. This act allows stem search research to counter Parkinson's disease, diabetes and Alzheimer's disease (30, 31) as they can be used for therapeutic purposes (32). The American Fertility Society is against the encouragement of this procedure. Immediately after the report of human polyspermic embryo cloning in 1992 (28), the Foundation on Economic Trends asked the National Institutes of Health to halt all funding of "institutions working on human cloning." The members of United States Congress were also called to make human cloning illegal in the United States and ordered to restrict completely IVF laboratories from creating any potential human clones regardless of the circumstances and the purposes. Recently President Clinton announced that all experiments with human gametes including cloning are illegal. It is very important that this technology should be controlled by legislation, or at least by governmental regulation; it cannot be left to the decision and practice of any individual or groups of scientists. Cloning by embryo splitting can be a useful and low-cost reproductive method for infertile couples and should not be condemned as an inappropriate technique just because we are afraid that the legal system is not strict enough to prevent scientists and patients from abusing it. We have been similar negative social critics in the past of IVF, sperm and ovum donation, and other techniques. However, the human need and correct logistic evaluations promoted their application in routine medical services. We believe that legal banning of cloning by embryo splitting in humans is based just on fears that this reproductive technique will be abused, without taking into consideration the tremendous clinical and cost benefits of this method. It is very important that human cloning be monitored under strict research protocols and supervision, but the trials should not be suspended.

CONCLUSIONS

Animal cloning by nuclear and embryo splitting should be continued. The potential benefits could be enormous: better-quality food at low cost, future drugs at reduced prices, production of human proteins, altered milk formulas for premature infants, etc. Nuclear cloning in human reproduction should be prohibited because there are no extra major benefits by its application. It can only create additional medical, ethical, and social problems. The potential of cloning by embryo splitting for minimizing clinical costs and risks as well as increasing the rate of success for couples who are infertile and having children for them is a challenge. Oocyte retrieval and Ovulation induction can be performed only once but there is no specific time period for transferring the cloned embryos. The minor legal and religious problems can finally be settled. If policymaker's guidelines win international acceptance and if they succeed, it may take less time to reach this goal. Cloning by embryo

splitting can have certain advantages in the reproductive performance of infertile couples.■

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