Human Cloning and Reproductive Counseling

Montse Boada
Institut Universitari Dexeus

Abstract

Scientists have been producing clones in amphibians, most notably in frogs, since 1954. In the early 1980's, experiments of nuclear transfer began to be performed in mammals culminating after much effort in the birth of Dolly, in 1997.

Even though I. Wilmut et al. and cols. consider that *«the gratest application will lie in the opportunity to introduce precise genetic change in the donor cells before nuclear transfer which will allow to study both the role of specific gene products and the factors regulating gene expression»*, cloning has given rise to many other concerns.

Although its efficiency and reproducibility in humans have not yet been proved, some people have already proposed the application of this thecnique to solve fertility problems. Artificial twining obtained from the division of preimplantation embryos has been suggested as a way to increase the number of available embryos in cases of poor ovarian response or in couples with a high risk of transmitting a genetic disease.

Not only embryo splitting but also real cloning has been considered as an alternative to natural or assisted reproduction. Some people consider that one day, an infertile or even a fertile couple might choose to have a child by cloning one or the other partner, and identify many reasons why people could be drawn to it: a desire to recreate one's partner, a desire to duplicate famous people or a «genius», or to improve the species.

All these assumptions lead to many questions with difficult answers and interesting ethical considerations. Is human cloning contrary to human dignity? Has everybody the right of reproductive choice?

The legal response to such speculations has been clear. On January 12th this year, in Paris, a total of 19 countries (Spain included) ratified the additional protocol to the Convention for the Protection of Human Rights and Dignity of Human Being of the Council of Europe, on the prohibition of cloning human beings.

Introduction

The possibility to create identical individuals for different purposes has been explored since the beginning of the 20th century. In 1952 Briggs and King described the early experiments on cloning, which consisted in the transfer of a nucleus from a frog embryo to an enucleated oocyte.

Since then, a number of embryos from several species of amphibia, fish, mice,sheep and cattle were obtained (Willadsen, 1989) using similar techniques, and it did not take long to see the birth of new individuals obtained by cloning. Thus, in 1968 Gordon described the process to obtain tadpoles from the intestinal cells of a frog and in 1981 three mice obtained by cloning embryo cells were on the cover of Cell. (Illmensee and Hoppe, 1981). The disclosure of the birth of «Dolly» in 1997 surprised the scientific community because for the first time differentiated adult somatic cells were used for cloning instead of the totipotent embryonic cells. This was followed by the birth of monkeys obtained by embryo splitting and by the cloning of calves and mice. All these advances entail a considerable methodological progress, as well as the promise of important applications in pharmacology and medicine.

Experiments on human embryo splitting carried out in the United States by Hall and Stillman (1993) were highly publicized, although the embryos were not viable because they were polyspermic. At that time, the possibility of applying cloning techniques to human beings resulted in some controversy, which has been recently an updated subject due to the statements of R. Seed from Chicago in the sense that he would clone a human being in 1999.

Cloning has not only been highly interesting for science but also for writers, movie directors and journalists, who have made it accessible to society, thus producing a lively social debate. Novels such as «A Brava New World», «In His image» and «The boys from Brazil» have made specialised technology available to the public, so that anyone without medical or scientific knowledge could understand such specialised subjects as cloning. As a result, everyone can come to his or her own ethical and social conclusions on this subject making use of their own judgement.

These considerations are likely to hold one of the opinions just mentioned.

Possible applications in human beings

Human beings could benefit directly or indirectly from the possible applications of cloning techniques.

In the agricultural field and in farm animal breeding, many attempts have been carried out to try to achieve the massive production of the best specimens using genetic engineering. Despite the negative consequences of the lack of diversity and tolerance against external agents, these methods can move considerable economic interests.

It is in the pharmaceutical biotechnology field where cloning techniques can become most useful. Several possible applications exist. One of them would be to use genetically identical

animals —obtained through cloning techniques— as experimental animals for clinical trials on drugs. However, its main applications would be related to gene therapy techniques. According to Wilmut et al. (1997), the main characteristic of cloning is that it allows to carry out precise genetic changes in the donor cells before the nuclear transfer to the recipient cells, so that the behaviour of the gene products can be studied, as well as the factors regulating gene expression.

However, not all applications are experimental. Some practical applications are cloning transgenic animals —which contain genetic material artificially transferred from another species— in order to produce at low-cost large amounts of specific proteins valuable in the pharmacology field, or animals obtained by cloning, which contain genetic material artificially transferred from other species, usually pigs, as a possible organ source for human transplantation.

Gene therapy through cloning is much more effective. Cloning animals has enabled to clone specific substances or tissues, as in the examples above. It is very important, however to differentiate between cloning proteins, cells, tissues or human organs and cloning human embryos or even adults.

What is meant by human embryo cloning is the use of cells from preimplantation embryos in the early stages before reaching the morula stage i.e., embryos in the early stages of development when the cells or blastomeres are still totipotent and have not started compaction nor cell differentiation. In these stages, the production of identical embryo is carried out by embryo splitting or separation.

Thus, eight genetically identical embryos could be obtained from an eight-cell human embryo (3rd day of *in vitro* development). These embryos would be as similar as are monozygotic twins, in the event that the embryos were implanted and eventually born. They would be genetically «identical», because they would all come from the same zygote. However, the somatic mutations that take place in the embryonic development would lead to differences among the clones. Besides, the influence of the environment should not be forgotten, because it has an enormous influence on the psychological and physical development of the individual. The interaction with the environment results in specific neuronal reactions and, with time, the accumulated experience could eventually modify two cloned individuals, which were originally identical.

Nowadays any embryology team experienced in micromanipulation techniques could use the embryo splitting methodology. It should be pointed out the embryo implantation after *in vitro* fertilisation (IVF) stands at around 18,2 % (Boada et al, 1987), and that the likelihood to obtain a viable embryo from a single blastomere is rather low. Although it has been proved that full term pregnancies can be obtained from a single blastomere (Veiga et al. 1987). Tarin et al. (1992) have shown that results become progressively worse when the number of blastomeres biopsied increases, and the remaining cell mass of the embryo decreases.

Applications of cloning human embryos are usually related to Assisted Human Reproduction. Human embryo cloning could be used to increase the number of available embryos through an *in vitro* fertilisation process in two theoretical settings: a) low number of mature oocytes to inseminate or b) low number of healthy embryos to transfer.

a) This situation takes place when the patient has a reduced ovulation, either from a poor response to ovulation stimulating treatments or because of a premature ovarian failure (Tanos and Schenker, 1998). The success of the technique depends on the number of oocytes to be inseminated and decreases with the number of embryos available to transfer. According to the 1997 figures given by the Institut Universitari Dexeus, while the percentage of pregnancy per transfer stands at 42,8 % when 3 embryos are transferred, it decreases to 7,5 % when only one embryo is transferred (Boada et al. 1977). Although these arguments seem convincing, in-depth study should be conducted to find out the possible advantages of increasing the number of embryos when there is only one embryo available, to determine whether pregnancy increased after the transfer of embryos obtained by embryo splitting. A poor response to stimulation is often related to a poor embryo quality especially in women of advanced age. In these cases, not even the embryo cloning techniques by embryo splitting would be of any help.

b) The second possibility is to use embryo splitting in Preimplantation Genetic Diagnosis (PGD)(Tanos and Schenker, 1998). PGD is performed in couples without any fertility problems but with a high risk of transmitting a genetic disease. *In vitro* fertilisation is carried out, and once the embryos have been obtained, an embryo biopsys is performed to establish, using molecular techniques, which embryos are healthy and can therefore be transferred to the uterus. The number of embryos suitable to transfer usually decreases considerably after diagnosis. Thus, the possibility of increasing this number through cloning has been suggested as one of the applications of this technique. However, one should consider in each individual case whether the advantage of increasing the number of embryos to transfer would compensate for the decrease in viability resulting from a new micromanipulation technique applied to an already micromanipulated embryo.

Leaving aside ethical and legal considerations, the existing scientific experience on human embryo splitting and on the eventual viability of the split embryos is not sufficient to support the inclusion of this technique in an *in vitro* fertilization programme. More conclusive studies are needed to find out whether embryo splitting would increase the number of successful cases in IVF programme.

The possibility of cloning individuals has been successfully used in farm animals. Since it has been carried out with mammals evolutionarily so close to man as monkeys, it is possible to imagine that cloning could also be successfully applied to humans, once the differences between monkeys and man have been overcome.

It would not be fair to think that there are no technical problems to be solved. Wilmut et al. (1997) needed 277 fused cells - i.e. enucleated oocytes fused with mammary gland cells that had been previously induced to quiescence to clone «Dolly». Out of the 277 fused cells, only 29 developed properly and could be transferred to carrier sheep for Dolly to be born (3.4%). The same authors obtained similar results when the donor cells were fetal or embryo cells (7.5% and 4.6% respectively), which shows that the efficiency of this technique has to be considerably improved before coming into practice. There are still many aspects to be solved, such as the high

rate of malformations and neonatal mortality in cloned animals, the capacity of reproduction of the new individuals, the possibility of premature aging, etc.

Several reasons have been put forward to clone human beings, that can be classified into two groups, depending on whether they are of social or personal interest.

The attempt at race selection or eugenics through the cloning of individuals with certain characteristics is socially unacceptable and legally prohibited.

Personal interests for cloning can be based on different reasons that can be classified according to their goals: a) self cloning or b) cloning another person.

a) Requests for cloning oneself can be motivated by a personal interest in perpetuation or by the absence of reproductive possibilities. Cloning can be seen as an alternative to natural reproduction by single persons (men or women), by homosexual couples or even by heterosexual couples with or without fertility problems

In general, the desire to clone oneself is closely related to the concept of immortality. One of the aims for cloning is making an individual's perpetuation possible, although, for the time being this is still impossible. In these cases, the individual usually has an exaggerated or a pathological degree of self-esteem.

b) Requests for cloning other persons may also be related to fertility problems. Homosexual couples might prefer cloning one of them instead of making use of assisted reproduction techniques (ART), which rely on donor sperm or oocytes.

Heterosexual couples with reproductive difficulties or elder couples, in whom the woman has reached physiological menopause, might consider cloning as an alternative to ART or adoption, although at present the latter are the only applications allowed and are much easier from a technical point of view.

Requests for cloning deceased relatives are also included in this group: children, brothers or sisters, husband or wife, etc, who died of a disease or an accident, have been murdered, etc. In the cases in which death has not resulted from an infectious disease, it is important to determine if the cause of death was hereditary or genetic; otherwise the same situation could be reproduced and the fate of the new clone would be inevitably identical.

Cloning famous people or a «genius» may entail not only a personal but also a social interest. It has been suggested as one of the possible applications of this technique.

Reproductive counselling

When analysing the possible practical applications of cloning techniques, some in-depth ethical reflections have to be taken into consideration. This may lead to questions not easy to answer: Does cloning attempt to human dignity?, Has anyone the right to choose its own reproductive option?, Is reproduction a right in itself?, Is it an individual or a social right?

We live in such a plural society that it is almost impossible to reach a consensus, since the different attitudes towards the subject are often conflicting. However, the representatives of such a plural society should define the limits of the new technologies after having been properly informed.

In 1988, cloning was already considered to be a very serious offence as recorded in the Spanish Law on Assisted Human Reproduction (ley 35/1988, section 20), and in 1995 the new Penal Code imposed a penalty of 1-5 years in prison for this practice, and up to 10 years of professional incapacitation for those who performed it (section 161). In both cases cloning is prohibited without further specification.

More recently and as a response to late events, the Council of Europe ratified in Paris, on the 12th of January of 1998, an additional protocol to the Convention for the Protection of Human Rights and Dignity of Human Being signed in Oviedo in 1997 which contains the explicit prohibition of producing identical human beings. Although this convention has not been ratified by all member countries, it was signed by a total of 19 countries, Spain among them.

The international response has been similar. In the United States, president Clinton asked for a 5-year moratorium, but other countries still do not have any law concerning this subject and they are not subject to any of the approved conventions.

Medical counseling should always include information assessed on the ethical and legal aspects of the procedure involved, to complement the medical information on the techniques given to the patient(s). In this way, the patients will be better able to reflect, analyse and decide on the situation. At present,there is no legal possibility to clone embryos or human beings in Spain. Should a request be made, information on the current situation should be given and alternative solutions offered. Although not all situations that may arise will have a legal alternative, many of them can be solved by current assisted reproduction techniques.

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