

## EDITORIAL

# Cloning and Gene Therapy: Where to Science is Taking Us

Fadheela Al-Mahroos, MD, FAAP\*

In February 1997 the scientists at the Roslin Institute (Edinburgh) led by Dr. I. Wilmut have astonished the world with the news about the birth of the cloned sheep "Dolly"<sup>1</sup>. In their experiment cells were taken from the mammary gland of an adult sheep, the cells were induced to become quiescent and the nuclei were transferred to an enucleated unfertilised eggs from a second sheep. Fusion of the donor cell to the enucleated oocyte and activation of the oocyte was induced by electrical pulses. Most embryos that developed to morula or blastocyst after 6 days of culture were transferred to recipients and allowed to develop to term. Dolly was the only successful outcome from 277 attempts.

The breakthrough in this experiment is the ability to induce the donor differentiated adult cell to exit the growth phase and enter the G0 phase of the cell cycle, this lead to changes in the chromatin structure that facilitate reprogramming of gene expression. This resulted in the transformation of a differentiated cell into undifferentiated stem cell that has the ability to develop to a variety of differentiated cells and organs leading to the birth of the full animal "Dolly". This has changed the long-held belief among scientists that the differentiation of cells is irreversible and that each cell shuts off most of its 150,000 genes and keeps active only those genes pertinent to the activity of that particular cell.

The birth of "Dolly" is an outstanding achievement which could revolutionize the approach to the management of several genetic and non genetic disorders. If proved to be true and reproducible it will open the horizon for new therapies that go to the root of the problem and it will irreversibly change the practice of medicine. However, it is important to be realistic and to maintain a degree of healthy skepticism, and to demand the need for more scrutiny and verification through more research.

It is important to note that Wilmut et al in the original paper published in Nature clearly state "we cannot exclude the possibility that there is a small proportion of relatively undifferentiated stem cells able to support regeneration of the mammary gland during pregnancy". In another word what is claimed to be an adult differentiated mammary cell may have not been more than a stem cell !

Nonetheless, the birth of "Dolly" has stimulated a great deal of controversy and the whole world seemed to be captured by the debate. This is understandable because the result of the study has an enormous scientific, social, ethical, economic and legal repercussions. For the scientific commu-

nity it represents a major milestone in science development. It has an impact not less than the impact of splitting the atom which began the nuclear age with all the good and bad that followed.

For the ethicist and religious people, it represents a threat to the family unit and public morality; it gives an alarming power to human-beings whom they believe "trying to play God". This is fueled by the debate in the gay and lesbian press who are trying to sell "Clone Rights" to preserve what they call "same-sex reproductive rights". The debate was further fueled by the announcement of the researcher Richard Seed about his plan to clone man; he sees human cloning as fulfillment of "God's plan for humankind is that we will become one with God" and that "man will become creator". For the pharmaceutical firms and the economist, it is an endless mine of gold.

Such far reaching and complex repercussion of cloning resulted in the mix-up of facts and fiction and provoked a lot of emotionally charged reactions. This mandates a thorough analysis of the issue from all aspects by all those concerned before jumping to hurriedly conceived and unplanned steps toward starting or banning cloning. One of the major challenges to the scientific community is to put before the public non-distorted facts about the potentials, limitations and the risks of cloning. Such a far reaching issue should not be decided in the laboratories and the public input is vital.

### What are the medical implications of cloning ?

From the medical perspective, the main impact of cloning is on **gene therapy**. Each human is controlled by about 150,000 genes responsible for every single trait and function in the body. Thus most of human diseases have genetic basis, few diseases are inherited through single gene, others are the result of several defective genes and far more diseases emerge through the interaction between genes and the environment.

Gene therapy is based on the manipulation of genetic materials to correct diseases due to defective genes. There are two types of gene therapy: somatic and germline gene therapy. Understanding the differences between the two is important to formulate an informed opinion about the potential application of cloning in treating human diseases.

---

\* Consultant & Chairperson  
Paediatrics Department  
Salmaniya Medical Complex  
Clinical Assistant Professor of Paediatrics  
College of Medicine & Medical Sciences  
Arabian Gulf University  
Editor, Bahrain Medical Bulletin  
State of Bahrain



**Somatic gene therapy** involves correcting the defective gene in the individual patient without the ability to transfer the modified gene to the next generation. This type of gene therapy is vigorously pursued across the world and the results of its application in man started to appear in 1990 for treating immune deficiency diseases.

**Germ line gene therapy** entails introducing changes to the human germline cells (ovum, sperm, early embryo). Such changes will be passed on to all subsequent progeny. From technical and ethical perspective this doesn't seem to be around the corner. However, the birth of "Dolly" and "Polly" and more recently, the calves "George & Charlie" is an indication that, at least from a technical point of view, it is not too far. "Polly" is a lamb carrying a human gene intended for producing a therapeutic protein in her milk, this protein is the coagulation factor used for treating hemophilia. The gene was introduced through genetically modified cell culture using the same nuclear transfer procedure which produced "Dolly".

More recently, in January, 1998 the calves "George" and "Charlie" were born, the two calves were cloned from the cells of cow fetuses. They carried a specific marker gene. They could help lead the way toward creating genetically altered animals that produce valuable therapeutic substances in their milk or as a source of immunologically modified organ donors which will not be rejected by the human immune system. Dolly was the only successful outcome from 277 attempts but for George and Charlie the success rate was about 1 out of 50 embryos, the rest were lost in the lab or while they were transported or the pregnancies failed.

The results of these studies confirm that the nuclear transfer method can be used for germline gene modification and that perfecting it is a matter of time and persistence. Obviously applying cloning in germline gene modification to human requires addressing the ethical and technical aspects. Many questions and risks should be clarified before embarking on any experiment in germline modifications.

The basic challenge to gene therapy is the delivery of genetic material to the patient cell in a specific and safe manner and that the transferred gene should persist for life and should lead to cure. Currently the vectors used are mainly attenuated or modified viruses. The disease causing part of the virus is removed or neutralised; the desired gene inserted and the byproduct is inserted into the patient. Many difficulties in the use of vectors should be overcome before gene therapy can move forward.

In a more recent development, in April 28, 1998, researchers from three major institutions in USA have announced that they have successfully treated Parkinsonism in rats by using fetal cells from cloned cows. This research is the first demonstration that transgenic cloned animal tissue can be used in the treatment of a disease. It is possible that cells from embryos less than a week old, perhaps cloned from the patients themselves, could be modified and then injected into the brains of patients with parkinsonism. These are very exciting and promising results but it will be some time before starting such therapy in man.

The current focus of investigators is the development of cloned transgenic animals to be a source of neural cells to treat neurodegenerative disorders and insulin producing cells to treat diabetes. Another focus is creating tissues containing specific antigens and immune modulators that will reduce the risk of transplanted organs rejection and reduce the need for immunosuppressive drugs.

Other major diseases which can potentially be corrected by gene transfer technology are cancer, severe immune deficiency disorders, hemoglobinopathies, juvenile onset diabetes mellitus and cystic fibrosis.

It is obvious that the potentials of cloning are tremendous and the challenges and risks are substantial. In addition, the risk of abuse is certainly present but the picture is clouded and confused further by the exaggerated reports of the media and some investigators. Thus it is imperative that the scientists be honest and inform the public about the potential uses, current limitations and possible consequences of gene therapy.

The debate goes on, and people on both sides of the argument have strong points to voice. But who should have the last word whether to continue or halt cloning in animals and/or human? Is it the scientist like Dr Richard Seed who lives in an Ivory-tower and thinks only about pure science and does not concern himself with the social and ethical implications of his research? Is it the religious leader who believes that any research that might interfere with the normal sexual reproductive process is a threat to mankind and should be halted immediately? Is it the political leader who might ban cloning if it is a politically popular decision? Is it the pharmaceutical firms which pursue profit?

Such conflict of interest should be clear in a very sensitive issue such as cloning. The decision about what to do and where to go should be a collective decision of all those responsible and concerned groups including scientists, legislators, politicians, religious leaders and the public. The debate should be opened and many pressing basic questions need to be answered before we can move forward and take decisions based on solid scientific and ethical rather than emotional criteria. Some of the pressing questions are:

- What are the potentials and limitations of cloning?
- What are the medical risks?
- What are the ethical, social and economic consequences?
- What are the possible misuses and can they be prevented?
- Does the potential represented by cloning outweighs the risk of possible medical and ethical consequences?
- Does the ethical concern justify impeding research in cloning that could advance the treatment or perhaps cure deadly diseases?
- Does the ban of human cloning stop it from happening?
- Is it ethical to exploit animals and let them suffer to alleviate human diseases?
- With the limited financial resources for providing "health for all" what are our priorities?

These and many more relevant questions remain unsettled and await further collective research study by all stake holders..