Ethical and legal controversies in cloning for biomedical research — a South African perspective

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Therapeutic embryonic stem cell research raises a number of ethical and legal issues. The promised benefits are new and important knowledge of human embryological development, gene action, and the production of transplantable tissue and organs that could be effective in reversing or curing currently irreversible disease processes. However, this research involves the deliberate production, use, and ultimate destruction of cloned embryos, hence re-awakening the debate on the moral status of the embryo. Other moral anxieties include the possibility that women (as donors of ova) would be exploited, that this research would land on the slippery slope of reproductive cloning, and that promises made too early could lead to false hope among sick patients. It also raises the question of intellectual and actual property rights in human cell lines and the techniques by which they are produced. Review of legal systems internationally reveals that there is no global consensus on therapeutic embryonic stem cell research. Legal considerations are very much influenced by ethical deliberations on the moral status of the embryo. The South African parliament is promulgating legislation permitting therapeutic cloning, thereby demonstrating a commitment by the state to act in the best interests of patients and of regenerative medicine.

S Afr Med J 2004; **94:** 906-909.

Commitment to scientific enquiry has led to research into human embryo stem cells for therapeutic goals. However, many ethical and legal issues are raised and the question as to whether or not to proceed with human cloning as a means to therapeutic ends is a morally serious and vexing one.[1] On the one hand, the medical profession and the public grapple with the promise that such research could lead to important knowledge that could benefit science and society at large. On the other hand, the moral complexities associated with such research require consideration as to whether there could be compelling reasons to limit or prohibit research in this field entirely.[2]

This paper briefly describes the sources of stem cells and the various forms of cloning. Ethical issues central to this debate are discussed. Disparities in legal systems internationally with regard to embryonic stem cell research are described, and the South African legal standpoint on the issue will be presented.

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Sources of stem cells and therapeutic cloning — scientific backdrop to the debate

Stem cells

Stem cells are tissue precursor cells that have the ability to self-renew and differentiate into more specific adult cells required in the body.[3-6] They are found at all stages of development and in most tissues.[3] Early human embryos (5 - 6-day-old blastocysts) comprise an outer cell layer from which the placenta develops, and an inner cell mass of in the region of 200 cells which gives rise to the fetus. This inner cell mass is the source of embryonic stem cells.

Totipotent stem cells are found in the embryo up to the 16-cell stage. These cells have the ability to form an entirely independent human being if placed in the uterus. The inner cell mass of the late blastocyst stage of the embryo comprises pluripotent stem cells, which have a limited ability to give rise to any type of specialised cell.[7] According to the South African Medical Research Council (MRC), research involving the use of totipotent stem cells is strictly prohibited. The MRC's view on pluripotent cells is that they are 'extraordinarily interesting to study'.[8]

Somatic stem cells are more committed or multipotent. Their differentiation is restricted to only one or a few tissue lineages. Although these cells have the ability to self-renew indefinitely, in general their frequency and versatility decline with differentiation. Self-renewal is especially low in mature organs.[3]

Potential sources of stem cells are fetal tissue that becomes available after an abortion, excess embryos from assisted

reproductive technologies, embryos created through *in vitro* fertilisation specifically for research purposes, and embryos created asexually as a result of the transfer of a human somatic cell nucleus to a denucleated ovum.[5] Other sources of stem cells are umbilical cord blood and bone marrow.[9] In addition, neural stem cells, haematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) can be harvested from fetal blood and fetal tissue.[10] Adult stem cells have been isolated from bone marrow, muscle, blood, liver and brain, where they function in tissue repair.[3] Adult bone marrow is also an easily accessible source of MSCs, which differentiate under specific laboratory conditions into fat, bone, cartilage, nerves and muscle.[11] Adult stem cells have so far been used for bone marrow transplants, skin grafts and the treatment of leukaemias.[12] Harvesting of adult stem cells is unlikely to cause controversy. However, the ability of these cells to reproduce is restricted, limiting their use for therapies.[13]

Cloning

'Clone' means a precise genetic copy of a life form.[8] The cloning of animal and human genes has been practised for many years.[14] Cloning at a molecular level involves the copying of DNA fragments containing genes and amplifying these in a host cell. The copying of somatic cells by growing them in culture results in cellular cloning. Utility here would be for the testing and production of new medical products.[14] Blastomere separation involves the splitting of the 2 - 8-cell embryo soon after fertilisation. Each of these totipotent cells is genetically identical. In nuclear transplantation cloning, the nucleus of a somatic cell is placed into an ovum, the nucleus of which has been removed.

The National Health Bill of the Republic of South Africa[15] defines reproductive cloning of a human being as the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose. Therapeutic cloning is defined as the manipulation of genetic material from adult, zygote or embryonic cells in order to alter the function of cells or tissues for therapeutic purposes.

The method of obtaining and culturing human embryonic cells indefinitely was described in 1998.[16] Just 2 years earlier, methods for the cloning of adult mammals using nuclear replacement techniques were reported in the scientific literature.[17] More recently, scientifically unsubstantiated claims of successfully cloned children have been reported in the press.[18-20]

The ethical debate — an overview

There have been mixed reactions to the prospect of cloning for biomedical research. It is supported by some for its medical promise, but opposed by others who view it as an intentional exploitation and destruction of nascent human life created specifically for research purposes, thereby undermining human dignity.

The moral status of the embryo

Society remains divided on the highly controversial issue of the moral status of, and what is owed to, developing human life. This divergence of opinion also poses an impediment towards arriving at a solution on what is owed to the cloned embryo. The moral status of the embryo was deliberated extensively but not resolved during the abortion debate. Neither was it unravelled during subsequent debates on certain forms of assisted reproductive technologies. The current debates on stem cell research are unlikely to lead to a solution on what is due to the embryo, as the essence of the debate remains unchanged and no new arguments have been forwarded.[21]

A review of comparative law on abortion and assisted reproductive technologies demonstrates the adoption of a middle position. The extreme views that embryos have no moral status and hence command no respect or that embryos have the same moral status as born human beings are not advocated. For instance, in South Africa an embryo has no legal standing until it is born alive.[22] However, once it is born alive it retains all its rights including those that were violated while it was *in utero*.[23]

Historically, sacrifice of developing human life has been accepted to benefit others. In the practice of obstetrics, the pregnant woman's welfare is paramount. A known complication of pregnancy is severe hypertension requiring immediate delivery despite a slim chance of fetal survival. In the past, some cases of obstructed labour were managed by fetal craniotomy. Even where the woman's life is not endangered, fetocide is practised in order to optimise survival for others.[24] It has been accepted clinical practice to forfeit one life in order to allow for the survival of others.[25] Selective abortion may follow as a consequence of prenatal diagnosis. Here the burdens associated with infants surviving with severe abnormalities are carefully balanced against the benefits of selective abortion to the potential person, the family and society. Hence, moral precedent already exists for subordinating nascent for more developed human life. These principles are also embodied in the Choice on Termination of Pregnancy Act[26] which allows for terminations of pregnancy even in the third trimester. Accordingly, it can be stated that in ethics and in the law, the embryo is not owed the same protections and rights as a born human being.

Deliberate creation of embryos for use in research

It has been suggested that the use of spare embryos from completed assisted reproductive technology (ART) cycles would be less problematic.[4] Arguments regarding the moral status of the embryo would apply equally to both types of embryos. Substantive argument can be made for the use of cloned embryos to avoid immune rejection problems.

Reproductive cloning – a slippery-slope issue

The line between therapeutic cloning and reproductive cloning

is quite clear. Despite the possibility that the technology generated could be misused, appropriate legislation permitting the former and proscribing the latter could be instituted.[1] South Africa has moved ahead on this.

Exploitation of women

Cloning for biomedical research would require ova from women donors. This raises concerns regarding the exploitation of women and re-opens debate on the co-modification of human body parts.[27] Hormonal treatment for the stimulation of the ovaries in order to produce excess ova is not without risk. However, the ethical codes regulating research on human participants are protective against harms. It is expected that intensive ethical review of proposals for cloning for biomedical research purposes would optimise subject protection.

Using ova from other species in creating stem cells by nuclear transfer techniques may be a way to overcome the problems of ova scarcity and the ethical issues associated with using women donors in this research. This possibility has met with scepticism from scientists despite an American firm, Advanced Cell Technology, patenting such a technique.[28] In addition, ethical problems associated with the moral status of the hybrid embryo may be easier to overcome than ethical problems associated with the moral status of the human embryo.

Raising expectations in seriously ill patients

Society has been promised extensive and instant benefits from stem cell research. It is morally unacceptable to raise false hope in gravely ill people. Researchers need to be honest in their public presentation of the benefits of stem cell research with regard to time intervals between theoretical possibility and clinical practice.[4]

Intellectual property rights

An additional ethical concern is that the techniques whereby human cell lines are produced and the results of the research could be patented, obstructing access to care. Apart from the concerns over transactional costs, there are questions as to whether the human body can be the subject of property rights and whether the human genome is actually the common heritage of mankind.[8] Legislation could be invoked regulating and preventing such patents.

Embryo stem cell research — medical possibilities and ethical imperatives

Chronic debilitating degenerative diseases including those of the brain (Parkinson's and Alzheimer's disease), pancreas (diabetes), liver (hepatitis), joints (rheumatoid arthritis), heart, lungs and kidneys and spinal cord injuries cause immense suffering to patients, their families and society. They also shorten lifespan and limit activity. Embryonic stem cell research may offer unique ways of investigating and possibly treating many of these diseases.[2,29] Creating embryos using nuclei from individuals carrying genetic mutations predisposing them to particular diseases could be used to develop an improved understanding and treatment of the diseases. Embryonic stem cells could populate unhealthy or dead tissue, differentiate, regenerate diseased tissue and compensate for loss of function or restore normal function.[2] Moreover, embryonic stem cells could benefit patients requiring transplants. The demand for organs for transplant procedures has steadily increased in recent times, with currently over 84 000 people waiting for organ transplants in the USA. The situation is worse in developing countries such as South Africa where not many people donate organs.[12] A further benefit of embryo stem cell research could be genetic therapy for genetic diseases as a result of the combination of cloning techniques and genetic manipulation.[30] Healing of burns and fractures could be accelerated. Cystic fibrosis, muscular dystrophy and other genetic diseases could be cured by using stem cells to deliver the missing protein or gene to target tissue.[3] So far, embryonic stem cells have been differentiated into functional neurons and beating cardiac muscle in the laboratory,[31] and MSCs have been given to children with osteogenesis imperfecta. In the latter, bone density has been noted to improve, and fracture frequency has reduced.[32] The possible medical gains of embryonic stem cell research are immense, hence an ethical imperative to proceed with work in this area.

Embryo stem cell research — regulatory and policy issues

In law the destruction of an embryo is not murder because the embryo is not regarded as a person.[22] Widely held philosophical and moral views hold that the status of a person requires further development, such as a nervous system capable of sentience. By day 14, the primitive streak, the first sign of development of the nervous system may be observed. Based on this, some countries permit research for specified purposes on embryos of less than 14 days. South Africa has opted for the 14-day limit.[15]

Reproductive cloning has been banned in many countries. Some countries have banned all forms of cloning without making a distinction between reproductive and therapeutic cloning. In the USA, Congress has banned federal funding for human embryo research. Research using private funds has not been proscribed.[33] Although the laws making their way through federal and state legislatures all aim to criminalise reproductive cloning, different approaches to therapeutic cloning have been taken.[34] Germany, Austria, Ireland, Denmark and France prohibit research on embryos requiring their destruction.[12] In Britain, research for infertility, contraception, birth defects and stem cell therapy is permitted on embryos until day 14 of development. Although reproductive cloning is banned under the Human

Fertilisation and Embryology (HFE) Act of 1990,[35] stem cell research using embryos was approved by an extension of the HFE Act in 2001.[13] In Australia, legislation varies between the states, with embryo research being banned in Victoria, but permitted in New South Wales and Queensland.[33] It is interesting to note that the USA, Germany and Victoria in Australia permit work on embryos imported from other countries.[12,33]

In South Africa, legislation prohibiting genetic manipulation of gametes and zygotes outside the body, and hence cloning, has been in effect for the last few decades.[36] The MRC in South Africa recommends that for the present, cadaveric fetal tissue and embryos remaining after completion of infertility treatments should be the only source of embryonic stem cells for the purposes of research.[8] It is the opinion of the authors that these recommendations are too restrictive and serve to stifle scientific progress aiming to benefit patients with irreversible and debilitating disease. Moreover, researchers in South Africa have a constitutional right to 'freedom of scientific research'.[37] Therefore, the freedom to research embryonic stem cells can only be restricted if such restrictions are 'reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom.[38] Given the conflicting approaches to the law in other democratic countries,[12] it may be difficult to show that such restrictions are unreasonable. However, the state is required to use the least restrictive means to achieve its objectives when infringing constitutional rights[38] and it could be for this reason that the national government reviewed its stance on the matter. Section 62(4) of the National Health Bill,[15] published in the *Government Gazette* in August 2002, allows for therapeutic cloning and embryo stem cell research on less than 14-day-old embryos. However, very strict regulatory criteria have to be fulfilled, including authorisation by the Minister of Health for work in this field. Section 62(1) outlaws reproductive cloning.

Conclusion

The process of healing has been accelerated as a result of the tremendous advances in biomedical research. Restrictions on the rights and freedom to research should only be for the most meaningful reasons, and as least restrictive as possible, in order to prevent damage to the scientific undertaking. Removing unreasonable prohibitions against embryonic stem cell research and encouraging work in this direction allows for society to benefit from the wealth of knowledge that will be created. The South African parliament has promulgated legislation permitting therapeutic cloning, thereby demonstrating a commitment by the state to act in the best interests of patients and of regenerative medicine (Act No. 61 of 2003). Here, there has been a partnership and not polarity between scientists and regulators. Legislative imprudence has not impeded scientific wisdom. Clearly, the message from South Africa is that it will be unreasonable to prohibit research using the technology of somatic nuclear transfer for therapeutic cloning.

References

1. The President's Council on Bioethics. *Human Cloning and Human Dignity: An Ethical Inquiry*. Washington, DC, 2002: 80-110. **www.bioethics.gov**.
2. The Advisory Committee on Health Research. *Genomics and World Health*. Geneva: World Health Organisation, 2002:; 107-173.
3. Fisk NM, Braude P. Stem cells. *The Obstetrician and Gynaecologis*t 2001; **3:** 211-212.
4. Holm S. Going to the roots of the stem cell controversy. *Bioethics* 2002; **16:** 493-507.
5. Lochner JdeV. The ethics of research on stem cells of human origion. *S Afr Med J* 2002; **8:** 54-57.
6. Austin TW, Lagasse E. Hepatic regeneration from hematopoietic stem cells. *Mech Dev* 2003; **120:** 131-135.
7. Weissman IL. Stem cells – scientific, medical and political issues. *N Engl J Med* 2002; **346:** 1576-1579.
8. Medical Research Council of South Africa. Reproductive biology and genetic research. *Guidelines on Ethics for Medical Research* 2002; **2:** 36-50.
9. National Bioethics Advisory Commission. *Ethical Issues in Human Stem Cell Research – Executive Summary*. Rockville, Md: NBAG 1999.
10. Campagnoli C, Fisk N, Overton T, Bennet P, Watts T, Roberts I. Circulating haematopoietic progenitor cells in the first trimester fetal blood. *Blood* 2000; **95:** 1967-1972.
11. Pittenger MF, Mackay AM, Beck SC, *et al*. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999; **284:** 143-147.
12. Schuklenk U, Lott J. Ethics, politics and stem cell research in South Africa. *S Afr Med J* 2002; **8:** 57-60.
13. Terada N, Hamazaki T, Oka M, *et al*. Bone marrow cells adopt the phenotype of other cells by spontaneous fusion. *Nature* 2002; **416:** 532-544.
14. National Bioethics Advisory Commission. *Cloning Human Beings – Report and Recommendations of the National Bioethics Advisory Commission*. Rockville, Md: NBAC, 1997.
15. The National Health Bill, Republic of South Africa. *Government Gazette* No. 23696, 8 August 2002. [B 32- 2003]. Section 62.
16. Thompson JA, Itskovitz-Eldor J, Shapiro SS, *et al*. Embryonic human cell lines derived from blastocysts. *Science* 1998; **282:** 1145-1147.
17. Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH. Viable offspring derived from fetal and adult mammalian cells. *Nature* 1997; **385:** 810-813.
18. The President's Council on Bioethics. *Human Cloning and Human Dignity: An Ethical Inquiry*. Washington, DC, 2002: 46-56.. (www.bioethics.gov).
19. Weiss R. Human cloning bid stirs experts' anger; problems in animal cases noted. *The Washington Post*, 11 April 2001; A1.
20. Brown D. Human clone's birth predicted; delivery outside US may come by 2003, researcher says. T*he Washington Post*, 16 May 2002; A8.
21. Harris LH. Ethics and politics of embryo and stem cell research: Reinscribing the abortion debate. *Women's Health* Issues 2000; **10**: 146-151.
22. Christian Lawyer's Association of South Africa v Minister of Health 1998 (4) SA 1113 (T).
23. Pinchin and another NO v Santam Insurance Co Ltd 1963 (2) SA 254 (W).
24. Evans MI, Fletcher JC, Rodeck CH. Ethical problems in multiple gestations: selective termination. In: Evans MI, Dixler AO, Fletcher JC, Schulman JD, eds. *Fetal Diagnosis and Therapy: Science, Ethics and the Law*. Philadelphia: JB Lippincott, 1988.
25. Savulescu J. The embryonic stem cell lottery and the cannibalization of human beings. *Bioethics* 2002; **16**: 508-529.
26. South African Parliament. Choice on Termination of Pregnancy Act 92 of 1996. Section 2 (1).
27. Cahill LS. Genetics, commodification, and social justice in the globalization era. *Kennedy Institute of Ethics Journal* 2001; **11:** 221-238.
28. Marshall E. Claim of human-cow embryo greeted with sceptism. *Science* 1998; **282:**1390-1391.
29. Solter D, Gearhart J. Putting stem cells to work. *Science* 1999; **283:** 1468-1470.
30. Rideout III WM. Correction of a genetic defect by nuclear transplantation and combined cell and gene therapy. *Cell* 2002; **109:** 17-27.
31. Itskovitz-Eldor J, Schuldiner M, Karsenti D, *et al*. Differentiation of human embryonic stem cells into embryoid bodies compromising the three embryonic germ layers. *Mol Med* 2000; **6:** 88-95.
32. Horwitz EM, Prockop DJ, Fitzpatrick LA, *et al*. Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. *Nat Med* 1999; **5:** 309-313.
33. Robertson JA. Human embryonic stem cell research: Ethical and legal issues. *Nature Reviews Genetics* 2002; **2:** 74-78.
34. Daley GQ. Cloning and stem cells – handicapping the political and scientific debates. *N Engl J Med* 2003; **349:** 211-212.
35. Campbell C. Ethical dilemmas of cloning. *Curr Obstet Gynaecol* 1998; **8:** 54-55.
36. South African Parliament. The Human Tissue Act No. 65 of 1983. Section 39A.
37. The Constitution of the Republic of South Africa. Act 106 of 1996. Section 16 (1)d.
38. The Constitution of The Republic of South Africa. Act 106 of 1996. Section 16 (1)d. Section 36(1).

Accepted 26 July 2004.