

The Ethical Validity of Using Nuclear Transfer in Human Transplantation

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THERAPEUTIC CLONING (OR CELL REPLACEMENT BY MEANS of nuclear transfer) is a new biomedical technology that has the potential to transform medicine. Therapeutic cloning involves the transfer of the nucleus from one of the patient's cells into an enucleated donor oocyte for the purpose of making medically useful and immunologically compatible cells and tissues (FIGURE).¹ Although the phrase "therapeutic cloning" has been most widely used in this context, we believe that it is misleading. "Cloning" brings to mind images of the replication of a single genome for reproductive purposes. In therapeutic cloning, however, no such replication is involved. For this reason, we prefer the term "cell replacement through nuclear transfer" (CRNT). In this article, we use both terms so that readers may become accustomed to the more technically accurate terminology. Moreover, because therapeutic cloning requires the creation and disaggregation *ex utero* of blastocyst stage embryos, this technique raises complex ethical questions.²⁻⁴ While these questions must be addressed and understood, we believe that a counterbalancing and stronger ethical case can be made for therapeutic cloning research.

Scientific Background

In November 1998, researchers at the University of Wisconsin, Madison, and The Johns Hopkins University, Baltimore, Md, announced the development of the first immortal pluripotential human stem cell lines.^{5,6} This research, which was hailed as the science "breakthrough of the year,"⁷ followed more than 2 decades of research on stem cells in mice and other animal models. Animal research has suggested enormous therapeutic potential for this technology. Cardiomyocytes generated in the laboratory from murine embryonic stem cells have been transplanted into the hearts of dystrophic mice where they formed stable intracardiac

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grafts.⁸ Mouse nerve stem cells have successfully reversed the progression of the equivalent of multiple sclerosis in mice and have restored function to the limbs of partially paralyzed rats.^{9,10} These findings suggest that cell transplantation therapies using such stem cells might someday provide dramatic new strategies for the treatment of a host of disease conditions. These include diabetes, liver and heart disease, neurodegenerative disorders such as Parkinson disease and Alzheimer disease, osteoporosis, blood cell disorders, muscular dystrophy, and injury caused by burns and trauma. There also is the possibility that these cells could be used to reconstitute more complex tissues and organs, including blood vessels, bones, kidneys, and even hearts.¹¹

If this research is to prove successful, many hurdles will have to be surmounted. Scientists will have to learn how to culture stem cells reliably in the laboratory and steer them toward development of the desired tissue types. It will have to be shown that these cells can be safely transplanted into the human body. Even if this is successful, major problems of immunological incompatibility and tissue rejection will remain. At present, the most promising sources of stem cells are early blastocyst-stage embryos or tissues derived from the gonadal ridge of aborted fetuses (embryonic germ cells). Incompatibility between these cells and the recipient may require the use of immunosuppression therapy. In the future, it may be possible to develop a wide variety of stem cell lines for transplantation and to select the lines that are most compatible with the donor. It also might be possible to manipulate the immunogenic factors in stem cell lines.

On a different front, recent research has shown that adult stem cells may be more plastic in their developmental potential than was previously thought¹²⁻¹⁴ and are capable of generating a diversity of progenitor cells for different lineages.¹⁵⁻¹⁷ Once the processes of cellular differentiation and dedifferentiation are better understood, it may be possible

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to grow in vitro adult stem cells derived from the recipient's own tissues.

Nevertheless, recent results emphasize the value of multiple alternative technologies. It has been found that when embryonic germ cells are implanted into early mouse embryos, the tissues containing the cells develop abnormally, leading to oversized fetuses and skeletal deformations.¹⁸ This suggests that these cells may have abnormal imprinting or are otherwise abnormal. As far as adult stem cells are concerned, it is unlikely that stem cells exist in the adult for all cell types and tissues. Where stem cells do exist, for example in the brain, it may not be practical to access them. In addition, the possibility of transdifferentiating adult stem cells—converting them into embryonic stem cells through direct cell reprogramming—seems remote at the present time and will require an understanding of the basic science by which DNA of a differentiated cell is reprogrammed into an embryonic state. Therefore, it is unclear whether any of the alternative research routes will achieve the desired therapeutic end in a timely manner.

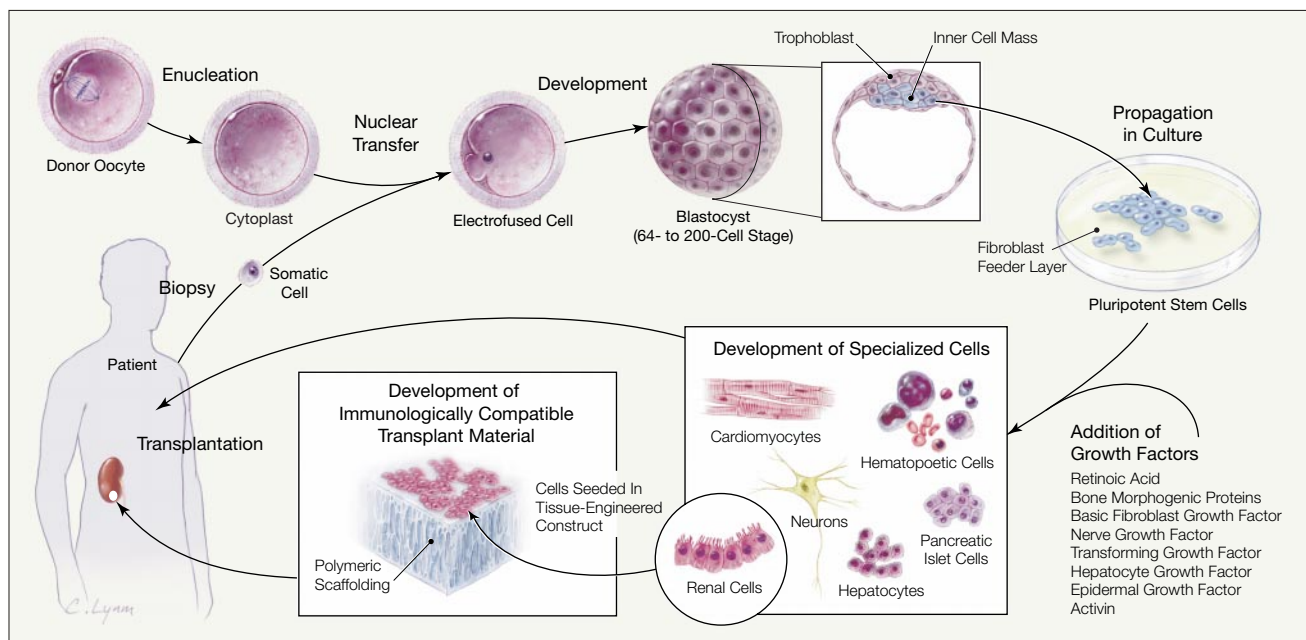
Therapeutic cloning promises an “end run” around all these problems. Since the early successes in the creation of animals by nuclear transfer¹⁹⁻²¹ and the celebrated cloning of Dolly in 1997,²² somatic cell nuclear-transfer (SCNT) techniques have been successfully used to clone a range of mammalian species.^{21,23-25} These successes suggest that it soon may be possible to produce viable human embryonic stem cell lines in this manner. Furthermore, because each of the cells in the

resultant stem cell line contains the nuclear DNA of the somatic cell donor, the transplant tissues are very likely to be immunologically compatible with the donor. Used in this way, SCNT technology promises an expeditious route to dedifferentiation and reprogramming of a donor's adult cells. As a means of understanding cellular dedifferentiation, this research direction is invaluable. In the longer run, CNRT may prove to be only a transitional technology that is replaced by adult stem cell transdifferentiation. But far from devaluing cell activation research, this transitional role renders it even more important in the immediate future.²⁶

Ethical Objections

Ethical objections to these technologies fall into 2 categories. The first, which pertains to all stem cell technologies using embryonic stem or germ cells, have to do with the manner in which these technologies appear to depend on the destruction of nascent human life, whether at the embryonic or fetal stages. The second set of objections is more specific to CRNT. Unlike much stem cell research, which can use spare embryos remaining from infertility procedures, CRNT requires the deliberate creation and disaggregation of a human embryo. Many people fear that this could lead to the “instrumentalization” of human life and the erosion of other research protections for human subjects. In addition, some worry that any cloning of a human embryo opens the door to the eventual cloning of a human being through the reproductive uses of this technology.

Figure. Procedure for Therapeutic Cloning



A somatic cell from the patient is electrofused with an enucleated donor oocyte. Pluripotent stem cells are isolated from the inner cell mass of the resulting blastocyst and then differentiated in vitro into genetically matched cells for transplantation. The cells also can be reconstituted into more complex tissues and organs using tissue engineering techniques.

Most who oppose human stem cell research using embryonic stem or germ cells base their view on the position that human life, in a moral sense, begins at conception. Those holding this position believe that from conception onward, the early embryo is the moral equivalent of any human child or adult.^{27,28} This means that an early embryo cannot ethically be used in research that risks its healthy survival. Embryonic stem cell research, which depends on the disaggregation of a human embryo, cannot meet this test. Because of embryonic stem cell research's close association with abortion, many holding this view also oppose embryonic germ cell research.

To most of those who hold this view, it does not matter that the embryos or fetuses used to produce cell lines are almost certain to be destroyed. They liken the embryo in these cases to a dying child or adult and believe that its circumstances call for enhanced, not reduced, research protections.²⁸ Most holding this view prefer research that aims at the development of adult stem cell lines, and they point to the promise of some recent results in this area. They also are willing to accept delays in the progress of stem cell research rather than permit the use of cell line sources that they regard as morally objectionable.^{27,28}

Some who hold the view that life begins at conception come to a different conclusion in which the use of embryos remaining from infertility procedures is concerned. Although they lament the creation of too many embryos in infertility medicine or the practice of abortion, they believe that no useful purpose is served by refusing to use the cells or tissues made available in this manner. They also reason that it is unlikely that the use of these cells or tissues in research will encourage either the creation of spare embryos in infertility medicine or abortion, since there are independent reasons these practices occur. For example, in 1996, 3600 embryos unwanted by their progenitors were destroyed in compliance with British regulations.²⁹ Until the efficiency of infertility procedures is increased, couples will routinely produce more embryos than they can successfully transfer or donate for adoption. US regulations prohibiting women from benefiting from fetal tissue donations appear to have reassured many people that the permission for such donations does not itself encourage abortion.

This limited acceptance of embryonic stem or germ cell research vanishes, however, when an embryo must be created *de novo* for a stem cell research protocol, as in the case of nuclear transfer. This makes this research particularly unacceptable to all those who believe that life begins at conception. It might be argued that an egg activated by nuclear transfer is not a human "embryo" in the traditional sense of that term, because it is not the result of fertilization. It also might reasonably be maintained that cell replacement therapy does not involve the destruction of an embryo but only its transformation into an embryonic stem cell line. After all, even in normal pregnancy, many embryonic cells do not develop into a fetus or child but become placental material instead. Nevertheless, most who believe that life be-

gins at conception will resist these arguments. They can be expected to extend their view to this entity as well as to the embryo created by nuclear transfer, on the grounds that its developmental potential is the same as a naturally fertilized egg. It is indicative of this way of thinking that existing federal regulations prohibiting federal funding of embryo research define the embryo as "any organism . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes."³⁰

In addition to this large body of opponents, some who do not share the view that life begins at conception oppose any research in which embryos are deliberately created and destroyed.³¹ These opponents fear the symbolic implications of the deliberate creation and destruction of a form of human life. They also worry that these practices could be the start of a "slippery slope" to the use of other classes of subjects in harmful research without their consent.

Replies to These Objections

Many people do not agree with the view that human life in a moral sense begins at conception. They hold a "developmental view" that sees prenatal life as increasing in moral weight over the course of a pregnancy and only reaching full equality with other human beings very late in pregnancy or at birth. Where the very early embryo is concerned, many considerations undermine the claim that it should be given substantial moral weight. Almost all views holding that human life begins at conception maintain that this is the moment when a new and unique human individual comes into being. However, because twinning and chimerism are still possible during the early stages of development,^{32,33} it is doubtful that one can speak of human individuality at this time.³⁴⁻³⁶ Developmental individuality, which is central to personhood, is not attained until the primitive body axis has begun to form and is associated with the morphogenetic migrations and proliferation of the mesoderm and notochord, known as gastrulation.

The early embryo's lack of organs also makes it unreasonable to believe that it is in any way capable of having thoughts, feelings, or experiences. This leaves the embryo's potential for development into a human being as the sole consideration justifying according it significant moral weight. It is not clear, however, how much this potential should count in justifying its protection. Most entities with potential to develop are not valued or treated in the same way as their developed form.³⁷ Eggs are not considered chickens and acorns are not considered oaks. The very high rate of early embryo loss also is relevant, with some estimates suggesting rates as high as 80% of all conceptions.³⁸ In most cases, the great majority of embryos will not develop into a human being. This loss rate reduces the force of the potentiality argument.

All these considerations support a developmental view that accords significantly lesser weight to the pregastrulation embryo and that justifies its use in research that could greatly benefit children and adults. Indeed, where research prom-

ises sufficient therapeutic benefit, this view may even morally require such research. Nevertheless, since an early embryo has some capacity for development into a human being, it is reasonable to accord it a measure of moral respect not given to other human bodily cells or tissues. In this context, respect means that research must be justified in terms of its scientific validity and likely therapeutic benefit. It also means that the number of embryos used should be minimized consistent with the need for the scientific validity of the study. This rules out the use of embryos for such things as routine testing for toxins, but it would justify their use in cell replacement research.

Some who accept these conclusions in which the embryo itself is concerned might nevertheless resist the deliberate creation of embryos for research on stem cells or CRNT through nuclear transfer. Some holding this position are persuaded by the argument that such practices might lead to the “instrumentalization” or “commodification” of human life generally.³⁹ To some extent, this argument presumes that the early embryo is human enough to warrant prohibiting its use as a source of cells or tissues. However, this assumption is rejected by a developmental approach that refuses to accord significant moral weight to the embryo before gastrulation.

This leaves for consideration only the various explicit and implicit “slippery slope” arguments invoked here. Such arguments typically hold that a practice that is not objectionable in itself may nevertheless lead to others that are clearly wrong.⁴⁰ This can occur because the line between a pre-gastrulation and postgastrulation embryo is not clear enough to anticipate that it will be long respected. Or the slide can result because the attitudes and practices established by such research habituate people and prepare them psychologically or socially for other, more worrisome practices. On neither count, however, is there reason to think that permission to create and use embryonic stem cells in research or the development of CRNT will lead to the predicted harms. The line established by gastrulation and the appearance of the primitive streak is a clear one, as is the line between therapeutic and reproductive cloning. It is unlikely that researchers working in properly monitored environments will blur these distinctions. It is true that the techniques developed in CRNT research can prepare the way scientifically and technically for efforts at reproductive cloning. But a halt to research on CRNT will not stop scientists’ intent on performing reproductive cloning and will only ensure that their efforts are even more risky than would otherwise be the case.

There also is no evidence that the use of embryos in research will lead to other human subjects abuses. Since 1990, Great Britain has permitted the use of embryos in research, including research involving the deliberate creation of embryos, and no such abuses have been recorded. On the contrary, it is reasonable to believe that where embryo research is permitted and monitored under carefully defined regulations, it is less likely that poor quality or ethically irresponsible research will occur.

All these matters lead to the conclusion that when its nature and purposes are understood, cell activation through nuclear transfer can command broad ethical support.

Legal Issues

Ten states have passed laws regulating and/or restricting research on human embryos, fetuses, or unborn children.⁴¹ Some of these prohibitions arguably apply to CRNT. Since the embryo has no legal standing in US constitutional law, however, it is doubtful that these statutes could withstand constitutional review. At the federal level, the Dickey-Wicker amendment forbids federal funding of any research “in which an embryo or embryos are destroyed.”³⁰ This appropriations amendment defines the embryo to include embryos reconstructed by nuclear transfer. In January 1999, the National Institutes of Health (NIH) legal counsel issued an opinion that the Dickey-Wicker amendment does not prohibit federal funding of research that “utilizes” embryonic stem cell lines so long as the actual derivation of these lines takes place under private auspices.⁴² On August 25, 2000, following a period of public review, the NIH issued formal regulations reaffirming this “use versus derivation” distinction and specifying that the NIH will only fund research on stem cell lines derived from embryos remaining from infertility procedures, not those deliberately created for research purposes.⁴³ Given strong congressional opposition to any funding for research that involves human embryos, there is reason to doubt that these regulations will ever go into effect. But even if they do, they rule out research on cell replacement by nuclear transfer because this requires the deliberate creation and destruction of a “human embryo” as this is defined by the law.

These restrictive regulations apply only to federally funded research. At present, outside of those states where embryo research is banned, private sector research on embryonic stem cells and on cell replacement through nuclear transfer is not illegal. In the wake of Dolly, bills were introduced in Congress that ban both human cloning and cloning research.⁴⁴⁻⁴⁶ However, none of these bills has passed into law. At least 6 states are considering cloning legislation that could potentially lead to the banning of CRNT.⁴⁷

Also in the wake of Dolly, President Clinton called for a voluntary moratorium on any privately supported attempt to create a human being through cloning.³⁹ This appeal does not have the force of law and does not apply to cloning research in which there is no intent to produce a child. It also appears that cell replacement by nuclear transfer will soon be permitted in the United Kingdom, where the Chief Medical Officer’s Expert Group has recently issued a report recommending that the Human Fertilisation and Embryo Authority (HFEA) modify its ban on human cloning to permit such research.²⁶

For the United States at least, we believe that the legal status quo is probably the best alternative possible. Given congressional opposition to almost all human embryo research, it is unlikely that the NIH will soon be permitted to fund any

research on human nuclear transfer. It also is unlikely that US scientists will see permissive unified public-private regulation in this area similar to the model of the UK HFEA. Although some have called for such uniform public-private regulation,⁴⁸ the divisiveness of anything touching on nascent human life in this country counsels against it. Such unitary regulations are likely to be held hostage to US abortion politics. It is sobering to recall that if present federal restraints had been extended to private sector embryonic stem cell research, none of the breakthroughs that mark this area would have occurred. Individuals who wish to see CRNT move forward, therefore, should probably resist efforts to extend the scope of existing state or federal laws to the private sector. The protection of gamete or embryo donors and the overall supervision of this research can be achieved through the existing tapestry of restraints that include the protections of civil law and professional standards of care, existing Food and Drug Administration regulations, oversight by institutional review boards when applicable, and guidelines provided by privately developed ethical advisory boards.⁴⁹ Relying on and reinforcing this framework of restraints is a more sound course than appealing for uniform federal guidelines that can only slow research or drive it overseas to more supportive legal environments.

Conclusion

Nuclear transfer is currently the most direct route to the development of cell replacement technologies that can prove of enormous medical benefit. Strong ethical arguments can be made that this research is not only ethically permissible but imperative. In the near future, those who favor this research should resist efforts to bring private sector research under state or federal control. Instead, they should work to reinforce and apply to it the existing framework for the protection of human subjects.

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