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Prospects and Perils for Humanity of Two New Genetic Technologies

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Abstract

Two new reprogenetic technologies are described - human reproductive cloning and germline genetic alteration. Some likely social and ethical consequences of their use are outlined, and a case is made for the development of international mechanisms to proscribe their use.

Introduction

Concepts from human genetics have greatly influenced social and political events in the last hundred years, and in turn, the direction of scientific development in human genetics and how it has unfolded, have been influenced and shaped by political and economic forces. Concepts from genetics were used and misused for political and social ends in much of the 20th century, with horrific programs resulting in the murder of millions of men, women and children. Some of the lessons that we should have learned from this, need to be kept in high focus as we enter the 21st century, because we are again facing some potential major misuses of genetics. The history of perversion and misuse of genetic science teaches us that genetic ideas can be misused to create a climate of thinking in which inhuman events become possible, because some people are seen as
genetically superior to others - who are seen as inferior. They eventually became classed as less than human, not deserving of the same rights as others.

How are these lessons relevant to the present time? In recent decades, there has again been a focus on genetics and genetic determinants of ill health and other traits. There have been billions of dollars invested in genetic research - everyone has heard of the Human Genome Project for example. During the same time period there have been many discoveries about the biology of human reproduction and its manipulation. We have now reached a stage where our technological capacities of manipulating genetic material and human reproduction, mean not only social uses of concepts of genetics, but actual uses of genetic technology may change what it is to be human. New reproductive and genetic technologies have many different uses - some beneficial, some not. This paper focuses on two new technologies in particular, which raise disturbing issues as to their consequences for humanity if they were to be accepted and used. One technology makes possible the other, and they have brought us to a choice point for the future of humans as a species. They are human cloning and germline genetic alteration.

To understand the ramifications and consequences that these technologies open up, it is first necessary to have some understanding of how biological development of a human proceeds.
Biology of human reproduction and development

All the cells in the human body contain the same genes - those genes came together when an egg carrying half the genes of the mother and a sperm carrying half the genes of the father united to produce a new entity, that after development, and many cell divisions, produced a human infant. But if all the cells of the body have exactly the same genes, why aren't they all the same? How is it that some cells are skin cells, some are brain cells, and some liver cells?

We come to be made up of different kinds of cells because during the time when eggs and sperm are forming, the genes in them are affected by factors in the cytoplasm of the sperm and the egg and the very early cells in development, so that some genes are programmed to turn off or be silent, while others are programmed to be active or expressed. As development proceeds, this programming process of the genes results in cells becoming committed to produce only a particular kind of tissue - because only those genes relevant to that tissue are expressed. After fertilization, the egg starts to divide and by the end of day 3 a cluster of cells about the size of a period at the end of a sentence has been formed. Until there are about 8 cells, each one of the cells in the cluster is still totipotent. That is, each cell, if separated and implanted in a uterus, is theoretically capable of producing a human with all the constituent cell types.

During the next couple of days the cluster develops a fluid filled space within it - it is then called a blastocyst. The outer cells of the blastocyst begin to
invade the uterus and will eventually become placenta, but one area of cells begins to divide to produce an inner cell mass. It is from this mass that the identifiable embryo itself will develop. By this stage, when it is about 150 cells, although each of these inner cell mass cells has lost its ability to be totipotent, it can still produce many types of tissues - it is pluripotent. A cell that can do this is called a stem cell. These are the embryonic stem cells that have been so much in the news, cells that can give rise to several different kinds of tissues that might be used to help people by restoring damaged tissue. As development proceeds, the cells of the embryo, then fetus, follow particular pathways of differentiation and become modified, so that some cells express only those genes that are needed to make skin cells, while others can produce only blood for example.

**Biology of nuclear transfer cloning**

The word "cloning" itself, simply means making multiple copies identical to the original. The word is used to describe growing many copies of a cell in culture - "cloning cells" - or it is used to describe making many copies of a gene by inserting it into a bacterium and having it replicated many times - "cloning DNA". However, the new technology that is being referred to when "human cloning" is used, is cloning by nuclear transfer.

Nuclear transfer cloning can be used to generate a whole new organism, and Dolly was the first animal to be made this way. To make her, the egg of a sheep was emptied of it's genetic material (the nucleus). This of course had
contained only half of the genes needed to make a sheep; the sperm would normally have added the rest. Into this emptied egg was substituted instead, the nucleus from an adult sheep cell containing all its genes.

The hope was, that the egg cytoplasm would reprogram the genes from the adult so that instead of being able to make only one cell type, the genes needed for development of all cell types would become reactivated. In essence it was hoped that the egg's cytoplasmic environment would make it revert to a totipotent stem cell, and give rise to an embryo with all its tissues. And once out of 277 times that it was done, the reprogramming worked well enough that Dolly was born. This technique has now worked to produce many mammalian species - cows, goats, mice, pigs, cats for example. There is no reason to think humans are much different with respect to this fundamental biology - it is likely humans could also be cloned.

There are many ethical reasons not to do nuclear transfer cloning to produce a child. There are real physical harms to potential replicands. All mammalian species that have been cloned have shown very high proportions of failures and deaths - heart defects, developmental delays, lung problems and malfunctioning immune systems. Some cloned mice that initially appeared normal, on reaching adulthood rapidly became grotesquely obese - on the same diet as normal mice. The best results are still not impressive, at less than 4% of animals born alive, and over a third of those dying shortly after.
These problems occur because transferring an adult nucleus into the egg does not allow the usual reprogramming of genes to happen properly. The usual "setting" of genes to turn on and off over development at the right time or place does not occur. Normally, in the months it takes sperm to mature, their genes are being reprogrammed, and a similar process happens in eggs, but over years. Unless this reprogramming is perfect, individual genes can go amiss at any time during development or in later life. With nuclear transfer cloning you are asking an egg cell to reprogram the inserted adult genes in minutes or hours.

The reprogramming of the transferred adult nuclear genes is unstable - and as a result the genes are expressed unpredictably over the animal's life course. Even cloned animals that seem normal in early life may have aberrations of gene expression later on - and it cannot be detected ahead of time what these will be. Because the nuclear transfer cloning process creates random errors in the gene expression program, it means the problems produced as the organism develops are quite unpredictable.\(^3\)

The biological reprogramming of genes is a fundamental process that is not understood and there has been little progress in solving it in animals over the last several years. The safety problems with reproductive nuclear transfer cloning are fundamental biological problems - they are not merely technical problems. Very extensive research would be needed to hope to understand it, and the problems may not be avoidable. Different species do this reprogramming
somewhat differently so it is not possible to simply extrapolate from animal work and assume it will be safe in people, and it clearly would be unethical to do such experiments in humans. The bottom line is human cloning from an adult's nucleus is unlikely to be "safe" in the foreseeable future.

These physical harms alone make it unethical to attempt to produce humans by nuclear transfer cloning. Clearly, they are not the only harms of this radically different way of producing people - which is replication, not sexual reproduction. However, this paper does not examine the additional social and ethical harms that arise from nuclear transfer cloning from an adult, as it is unlikely to be taken up by many people. There are very few situations in which people, in practice, are likely to undertake the risks and costs of this way of having a family. But quite apart from the physical harms, and the additional potential social and psychological harms of producing people this way, a critical aspect is that nuclear transfer cloning opens up realistically for the first time, the possibility of genetically engineering humans. And it is this conjunction - of one technology enabling the other - that is dangerous for humanity.

**Biology of germline genetic alteration**

The second genetic technology I referred to is germline genetic alteration. Germline genetic alteration involves making a change in genes in eggs, or in sperm, or in very early embryos, so that as a consequence the ovaries and testes
that later develop in the resulting individual also have changed genes. The important thing about such genetic alterations is that they are passed on to any offspring and then to their offspring. This is in contrast to genetic alteration which changes the genes in body cells only - in the blood, or liver, or brain for example. Such somatic genetic alteration, since the change does not affect eggs or sperm, is not passed on to children. For example, someone having gene therapy for a blood disease would not pass on genetic changes in their blood cells to their children.

The major impetus to developing nuclear transfer cloning for producing animals, has been that it would make possible germline genetic engineering to give animals desired traits. Animal cells are cultured; genes are inserted into them in the lab, the cells in culture are screened to see which cells have successfully incorporated the gene. Only those cells that have incorporated the desired genes are used as the donors of nuclei to make cloned animals. Genetically engineered cloned animals can be created this way with commercially desirable genetic traits. It is possible for example, to insert genes for heavier meat yield, or genes to make domesticated animals produce insulin in the milk for a pharmaceutical company, or genes to make them produce spider silk. Transgenic animals are now relatively common place. Dolly's maker, Dr. Ian Wilmut, has himself said that cloning an animal was done for two reasons - "to find out how cells work" and because it was "a technology that enables true genetic transformation of animals". Nuclear transfer cloning is a means that makes genetic engineering of animals possible. It
is a means to an end - but what may be suitable ends in animals may not be in humans.

Replication by cloning makes it possible for the first time to think in a practical way about genetically enhancing humans. Couples could be offered the chance of having a genetically improved child. It would be expensive, but it is possible it will be feasible in future. How would it work? A couple would have in vitro fertilization, and the embryos be grown in the lab to the stage where there are inner cell mass cells - the embryonic stem cells that can be taken out and grown in the lab. These cells would be cultured in vitro and the desired gene or genes inserted into them. Those cells successfully incorporating the gene would be used to supply the nucleus to an emptied egg from the woman. It would then be implanted in her uterus. Since the nucleus comes from a very early developmental cell that has gone through the gene programming process, it may prove more successful, and possible to avoid the problems of using an adult nucleus.

This variation of human cloning does not have the usual property that the offspring is simply a replicand of one of the parents. The child is actually a replicand of the embryo that gave rise to the embryonic stem cells. The couple therefore are able to have a child related to them both, but because it makes genetic alteration possible, it may become possible to also have a so called "improved" child with enhanced attributes. Because it is done so early in the
development of the organism, before the ovaries or testes are even formed, the altered genes will be present not only in body cells of the resulting individual but in the eggs or sperm they produce as an adult. This means the genetic alteration, or so called "improvement" is passed on down that line. It is germline genetic alteration. In future, for example, genes related to height or to intelligence could be inserted, or genes for viral-disease resistance, or genes to protect against degenerative diseases.

**Potential social consequences**

If human nuclear transfer cloning to produce a human is permitted, what will stop such germline genetic "enhancement" being used? There would be strong individual motivation on the part of some to have a taller or disease-resistant child. The idea you could add genes to your baby that gave them an advantage, might appeal to significant numbers of people. Facilities providing this would benefit financially and if it is allowed, it is likely to be marketed. The technology could spread, based on individual choices and market forces. Advertising and promotion could lead to use - at least for those who could afford it. History shows us that acceptability can be changed by aggressive marketing and promotion. The billions of dollars spent by the tobacco and pharmaceutical industries are not spent in vain - they clearly lead to increased consumption as a result.
Is there any evidence as to whether some people would want to use this? Athletes take various drugs and hormones to give them an edge, even though they know this could have serious long term adverse effects on their health. Some parents in the U.S. pay $14,000 a year for growth hormones for their child who is at the lower end of normal variation. Some people clearly value highly what they see as a competitive edge in their children - some individuals have purchased desirable eggs for $50,000. We have seen how mass marketing and advertising has been successful in generating a large cosmetic surgery industry. If genetic alteration is promoted as offering the chance to look better or have a competitive edge in performance, it is likely a proportion of people will want to take it up.

Let us assume a minority do. Those "improved" individuals who are taller or smarter, are likely, on average, to do better in life and be able to have not only better educations and jobs, but as a consequence be able to buy additional, further refined genetic "advantages" for their progeny as these become available in future decades. Such people are likely to preferentially marry others like themselves. Eventually, over generations, the human population may start to diverge into the genetically engineered advantaged and the rest. This path creates two classes of humans, one viewed as more desirable or worthy than the other. The new "improved" individual would almost certainly come to represent the superior class and the rest of humanity the other, less desirable. It has been suggested that these technologies could mean humans diverge over time into two species. This could
come about over time not by being imposed from above, but by individual choices in a market place where this technology is available.

Some scenarios for human cloning - such as that a dictator could clone groups of soldiers to serve the state, or that geniuses such as Mozart would be duplicated are not very likely. In the first scenario, there are easier ways to get troops without waiting for 20 years, and in the second, duplicating a specific attribute such as creativity in music which is strongly influenced by environment, is unlikely to work. Genetic engineering might make it more likely someone would be musical, but staggering genius is unlikely to be reliably duplicated. However, theoretically, genetic enhancement could improve any trait that is partly determined genetically - including those that are multifactorial and affected by the environment, such as height or intelligence. In 1999 a Princeton scientist used genetic engineering to create mice with better memories, who learned faster.\textsuperscript{14, 15} Other scientists are working on identifying genes associated with general cognitive ability - quantitative trait loci that contribute probabilistically to individual differences in the normal variation in intelligence. Genome scans looking at several thousand DNA markers, and microarrays are being used. Workers in the field predict that several relevant genes will be located.\textsuperscript{16, 17, 18}

In future, even if a minority choose to use I.Q. enhancements there would be enormous pressure on the rest of us to do so. As noted economist, Lester Thurow of MIT has said "Suppose parents could add 30 points to their children's
IQ. Wouldn't you want to do it? And if you don't, your child will be the stupidest child in the neighbourhood”. The real interest in the general population in cloning will not be for copying particular adults. It will be if it is combined with genetic "enhancement" to give a child what is perceived to be a better chance in life. The idea you could add genes to your child to give it an advantage over others might be appealing to many parents who could afford to pay for it. Use of this genetic technology would put into play an unprecedented set of social, economic and political drivers that could interact to produce unintended consequences. These technologies alter an individual's genetic material and thereby shape not only one person's life, but are passed on, and affect all subsequent generations of that line. Starting to directly alter genes that are passed on into the human gene pool would be a radical new step.

Nevertheless, some scientists are eager to go down this road, as the following quotes illustrate:

James Watson, Nobel Laureate and Founding Director of the Human Genome Project: "….no one has the guts to say it, if we could make better human beings by knowing how to add genes, why shouldn't we? What's wrong with it? Evolution can be just damn cruel, and to say you've got a perfect genome and there's some sanctity? I'd like to know where that idea comes from, because it's utter silliness".20
Lee Silver, Professor of Molecular Biology and Neuroscience at Princeton University. "…the gen rich class and the natural class will become entirely separate species with no ability to crossbreed, with as much romantic interest in each other as a current human would have for a chimpanzee. But in all cases, I will argue, the use of reprogenetic technologies is inevitable. Whether we like it or not, the global marketplace will reign supreme".13

Professor Gregory Stock, University of California, Los Angeles: "Altering the genome is essentially the endpoint of the whole genomic revolution".20

The possibility of using genetic technology on humans to make them smarter, taller, longer lived, disease resistant etc. raises many issues.21 If we go down this path we would be taking human evolution into our own hands. We would become products of our own manufacture and would be claiming a new eugenic "right" to make of our children what we desire.22 If we go down this path, what will humans be like a 1000 years from now? Is this path compatible with a just society, with equality of opportunity, and respect for difference? Genetic diversity contributes directly to the richness of humanity, and in this kind of world is likely to be devalued.

The costs of these technologies mean that if permitted, only some are likely to have access. Dr. Silver has predicted that the gen rich class which would emerge, would control the economy, the media and knowledge based industries.13 He sees most unaltered humans working as labourers or service providers, and
foresees the two groups, inevitably, over many generations becoming separate species. He thinks this will happen because in the U.S. citizens value individual freedom very highly and think that if they have the money they should be free to pay for such technology. He finds no legitimate reason to restrict the use of reprogenetics, and so he foresees that the market will determine events.

Unless the government were willing to underwrite it, genetic changes that could enhance life chances, would be available only to those who had the financial resources to have access. These technologies would have to be provided as a socially underwritten "good" if they were to be available not just to a privileged few, but to everyone. It is unlikely that most countries would be willing to provide them, but even if these technologies were made available as a "public good" in order to ensure equality of access, government would then have to decide for what traits people may have access. What would they be? Docility? Height? Who would decide? Transparent criteria would be needed, with public input, as well as a regulatory body.

History shows us that where there is perceived individual benefit from a new technology, and the ability of some to pay well to obtain it, unless there is legislation, there will be professionals willing to provide it. There is a billion dollar private reproductive medicine sector in the U.S. and in that market-driven context unless legally prohibited, these technologies are likely to become available. You can for example, currently peruse catalogues if you wish to buy
human eggs. Forgotten in all this technology drive is that we already know how to improve our children's lives - parental investment, good nutrition, good prenatal support, clean air and water, and accessible education. These are the policy paths that need to be pursued, not the path of genetic enhancement.

I believe it would be disastrous to leave these uses of genetics simply to market forces. Permitting nuclear transfer cloning to make human embryos and permitting their genetic enhancement would inevitably lead to social inequality and to unfair advantages by the enhanced for desirable resources and status. A policy context where the market is left to decide what can be done with reprogenetic technologies would result in great social harm, driven by individual, not state, decisions. Individually beneficial decisions in this case may lead to very harmful social consequences. The likelihood of injustices and violation of human dignity are too great not to have social policy on this. Having no policy is a policy because in a policy vacuum, the market will decide.

**International policy implications**

What are we to do at the lip of this whirlpool? The worldwide revulsion at the prospect of cloning humans needs to be built on, and citizens mobilized, to ensure we do not misuse these technologies and change the nature of humanity. Some have written that use of these technologies in humans, in a sense, can be viewed as a "crime against humanity". Human dignity and social justice are only likely to be safeguarded if this area of technology use in humans is
accountable to limits and to oversight in a democratic way. It should not be up to an individual country, an individual company, a particular clinician or researcher to decide to manipulate the human germline or replicate people. No individual scientist or corporation has the moral warrant to decide to manipulate the human germline or replicate people. Technologies that change the species and have far reaching consequences mean populations worldwide have a legitimate voice in deciding whether or not they will be used. The decisions should not be taken pre-emptively by a particular clinical facility or a particular group of scientists who ignore the wishes of the rest of us. We need international institutions and mechanisms to be put in place so people from many countries may have a voice.

Nuclear transfer cloning to produce humans should be prohibited in a worldwide treaty. Germline genetic alteration should also be subject to international oversight. The prospects of making human beings by cloning has elicited deep concern in many countries, and there have been calls for a worldwide ban on cloning used to produce humans by many political and religious leaders, as well as by organizations such as the World Health Organization, the World Medical Organization, the American Medical Association, and UNESCO. Nineteen countries in the Council of Europe have signed an agreement that bans human cloning. The U.N. General Assembly has struck a committee to develop an international convention to prohibit cloning of humans. However, as yet there is
not much public awareness of how cloning and germline alteration could be used in conjunction; this is an issue that has yet to come into public consciousness.

Although the joint uses of these technologies are not yet possible in humans, given the pace of discovery and given what is possible already in animals, such scenarios cannot simply be dismissed as science fiction - they are possibilities we may have to deal with in the future. It is important that the public become aware of the choices with regard to genetics we may have to make, and that they become involved in deciding what limits are needed. Not only biotechnology companies and scientists should be engaged in these issues, civil society needs to be involved. If we take the position that everything that is technologically possible should be permitted, provided parents are free to choose - we will be sucked down into the whirlpool and a non-human future. There needs to be a way of framing the issues in the public dialogue that takes into consideration not only individual autonomy, but long term social consequences.

**Widening the frame**

Much of the debate on human cloning focuses on weighing harms and benefits to individuals. This is dangerously incomplete. Looking at the issue as a reproductive technology choice has the consequence that many issues are completely left out of consideration. We need to shift to a framing that shows how permitting germline genetic alteration and human nuclear transfer cloning would affect not only the individual making the decision, but future generations.
and our society as a whole. Even though initially, individuals on whom these technologies had a direct impact would be a minority, it would be likely to grow. Viewing cloning as a personal, private matter inappropriately minimizes the potentially serious social consequences - yet these wider consequences need to be taken into account, because we all have a stake in what kind of community we live in. We don't want it to be one where children are not valued for themselves but commodified, and one where social injustice is inevitable. These two technologies, used jointly, raise profound issues about the future of our species. We are unlikely to have the wisdom to direct our own evolution appropriately when we have not yet found the wisdom to deal with hunger and environmental degradation.

The use of cloning with genetic enhancement focussed only toward individual wishes will result in social harms because the interests of the individual and the public good differ. There is an analogy with the Tragedy of the Commons where each rancher sharing common grazing land, or each fisher sharing a fishing ground, has an incentive to overgraze or overfish because the benefits of doing so accrue to them as an individual, whereas the eventual costs and harms accrue to the whole community. The cumulative impact of individual centred choices can result in an unethical system. Even individually advantageous choices, in aggregate, may harm the long term common good.
Conclusion

At heart how we use these two technologies is not an individual or medical matter, but a matter of social policy. If we chose to permit them, it is likely their use will further entrench existing inequalities, create new ones and threaten human rights. The moral and ethical lessons we should have learned from the past century about misuse of genetics will have gone unheeded. Those lessons are a cogent reason for us to avoid using these technologies, which we know will generate consequences beyond our control. We could end up with a divided and inhuman society, without that being the intention. Technological prowess is not the only measure of a civilization. We are a social species, and need to value others and be valued in turn to be fully human. We need to recognize the importance not just of individual autonomy to make choices, but that there are some choices that society should make, because the consequences would be so detrimental to us all and to how we relate to each other. Which path we choose to follow is important to the future of our species. I hope we deal with the choice wisely.
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