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viewpoint

Reprogenetics: third millennium speculation

The consequences for humanity when reproductive biology and genetics are combined • *by Lee M. Silver*

On July 25 1978, Louise Joy Brown, the first baby to be conceived outside the human body, was born. Her birth made headlines as it showed that *in vitro* fertilisation techniques could provide a cure for infertility, helping couples who otherwise could not conceive. But Louise Joy Brown's birthday represents a singular moment in the history of humankind for another reason: science had brought the human embryo out of the darkness of the womb into the light of the laboratory.

Today, *in vitro* fertilisation has become a commonplace service. The best IVF clinics offer their customers success rates of up to 70%—twice as high as that naturally achieved by fertile couples actively trying to have a baby. At the same time as assisted reproduction techniques have been improving, there has been an explosion of knowledge in genetic research and technology. The 'Human Genome Project,' will eventually identify each and every human gene and characterise how it interacts with other genes and with the environment. The results from this immense undertaking will allow researchers to determine how individuals differ at each of these genes and how these variations influence unique personal characteristics. These differences will include resistance or susceptibility to infectious and inherited diseases, as well as the efficacy of drugs or therapies (Kruglyak, 1997). With ever-increasing knowledge, biologists will ultimately be able to make connections between genetic profiles and physical or mental attributes that we commonly refer to as innate talents.

New genetic technologies have implications for all fields in medicine, but when they are combined with reproductive technologies, the prospects are staggering. Indeed, the combination is so different from that of either technology alone that it deserves a new appellation: *reprogenetics* (Silver, 1998). Reprogenetics refers to the use of genetic information and technology to ensure or prevent the inheritance of particular genes in a child.

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Humans have always practised reprogenetics. At the simplest level, people look at a potential marriage partner and ask themselves, 'Do I want to have children with this person?' Whether conscious or not, a marital choice made on the basis of this question will have a real effect on the alleles that a child receives.

One step higher in technical sophistication is the selection of a sperm donor. Artificial insemination has been used for over 100 years to overcome infertility, and now some 50 000 children are born each year through the use of this procedure. The choice of the sperm donor has never been random. In the past, physicians selected donors based on health status, family history and other traits considered desirable such as intelligence, athleticism or character. Today, parents who need donor sperm can choose from catalogues on the World Wide Web. Similarly, egg donation is used in cases where a woman is unable to produce her own. The demand for egg donors with 'superior qualities' is so large, and the number of women willing to donate eggs is so small, that 'supply and demand' economics have taken over this process in the USA. A recent advertisement in the Princeton University student newspaper offered $50 000 for eggs from a woman meeting certain criteria. Of course, many desired characteristics have little chance of being inherited, but the simple fact that people try to control their children's genes is a sign of reprogenetic intent.

Finally, any time a woman decides to abort a foetus based on the results of amniocentesis, she makes a negative choice against certain alleles in her unborn child. And any time an abortion is chosen solely because a child would have been mentally retarded, reprogenetics is being practised for the one purpose of increasing the intelligence of the child that is ultimately born through a later pregnancy.

Many bioethicists oppose all attempts by parents to actively control the genetic makeup of their children. They equate reprogenetics to clearly abhorrent

eugenic practices used in the past. But in fact, reprogenetics and eugenics are fundamentally different from one another, both in terms of control and purpose.

The purpose of eugenics was to improve a society's so-called 'gene pool' by controlling the breeding practices of its citizens. In the early twentieth century, the USA put this idea into practice by the forced sterilisation of people deemed genetically inferior because of supposedly reduced intelligence, minor physical disabilities or criminal character. Further 'protection of the American gene pool' was endeavoured by congressional enactment of harsh policies to restrict the immigration of people from Eastern and Southern Europe—regions whose populations (from whence all four grandparents of the author of this paper came) were considered to harbour undesirable genes. Eugenic practices were not restricted to the USA, but were also used in Sweden and more recently in China where mentally retarded people were sterilised. Nazi Germany's version of eugenics was the most horrendous one, eliminating all those who were deemed to carry any undesirable genes. In the aftermath of World War II, with the repulsion against the atrocities committed by the Nazis, eugenics was finally and rightly repudiated as discriminatory, murderous and infringing upon the natural right of humans to reproduce freely.

While eugenics is controlled by the government, reprogenetics can be controlled at the level of individual prospective parents. And while eugenics is concerned with the vague notion of a societal gene pool, reprogenetics is concerned with the very real question of what genes an individual child will receive. While the promulgation of eugenic practices led to a restriction of reproductive freedom and worse, reprogenetics will do exactly the opposite. It could give parents children with a higher likelihood of being healthy, without bringing direct harm to anyone else.

Fundamentally, reprogenetics can be understood through its sole motivation: the desire of parents to give all possible advantages to their children. Indeed, this evolutionarily derived instinct is expressed by parents of many species who use all available resources to maximise their children's survival chances. Reprogenetics allows parents to reach for this goal before their child is even born. Affluent parents provide environmental advantages for their children after birth; reprogenetics will allow them to add genetic advantages. It is important to point out that both genetic and environmental advantages simply enhance probabilities—nothing is guaranteed. But the lack of guarantee does not stop parents from spending $150 000 to send their children to Princeton University.

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If democratic societies allow parents to buy environmental advantages for their children, how can they prohibit them from buying genetic advantages, as both are aimed at the same goal of helping a child? If reprogenetics is used to increase chances of health, happiness and success, what could be wrong with it? I will not answer this question now. Instead, I will first consider future reprogenetic technologies and the potential impact on naturally existing biological inequities.

Two reprogenetics technologies based on the use of IVF are currently available: embryo selection and genetic engineering of the germline. For embryo selection, DNA analysis is performed on a single cell taken from an 8-cell human embryo. Thus, once certain genes are characterised, for example, parents could select embryos that will develop into taller children, or children with increased potential for longevity or long-term happiness—which has a strong genetic correlate. Embryo selection does not involve modification of the genome, it just allows parents to select one embryo over another. It is equivalent to placing the dice on the table rather than throwing it for a random reproductive outcome.

However, embryo selection is severely limited as a reprogenetic technology for two reasons. First, if parents do not carry a particular allele, none of their embryos will either. Secondly, parents can choose to select any allele, but they cannot choose many. Because our genes are reshuffled like cards before we hand on 50% to our child, the probability that any one embryo will get any set of alleles decreases exponentially as the gene number increases. Simple probability calculations suggest that it will never be feasible to select more than five genes. Since traits like height, health and personality are influenced by large numbers of genes, it is unlikely that embryo selection will ever go beyond avoidance of simple genetic diseases.

All of these limitations disappear with genetic engineering of the germline. Any gene imaginable and any number of genes could be modified in, or added to, an embryo. Over the last 20 years, the technology of germline engineering has been used with increasing efficiency to alter embryos in a variety of species—including mice, pigs, and sheep—in an increasingly sophisticated manner (Hogan *et al.*, 1994). Until recently, however, the possibility that this technology might be applied to human embryos was not given serious consideration because of three major problems. First, the technology was extremely inefficient, with success rates typically less than 50%. Secondly, the application of the technology was associated with a high risk of newly induced mutations. Finally, there was—and still is—a general sense that genetic engineering can never be performed on people because of the possibility that a particular modification might

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have unanticipated negative side effects. The existence of any one of these problems alone would be sufficient to label genetic engineering of the human germline as unethical and irresponsible.

But as we move into the new millennium, the technological landscape is improving dramatically. It now seems possible that all three problems can be overcome. Powerful new modification and screening technologies could soon allow scientists to alter the genomes of embryos and identify only those in which the desired genetic change has been implemented without any damage to the pre-existing genome. This technical advance could eliminate the first and second problems associated with genetic engineering. But the third problem seems to remain. Even if the embryo's genome is engineered exactly as intended, how can we rule out unintended, unanticipated and deleterious side effects?

Before we can answer this question, we must understand that while there is a near-infinite number of possible germline genetic modifications, they can all be placed into two categories. Type I genetic changes are those that provide the embryo with a genotype substantially equivalent to one that people receive naturally. Type II genetic changes provide enhancements that no human beings receive naturally.

Geneticists now understand that people are not born equal when it comes to biological properties including physical and physiological characteristics, disease resistance or susceptibility. One percent of the population, for instance, carries a mutation that provides absolute resistance to HIV infection. Some people have superior cancer protection genes, and others are born with alleles that greatly increase their life expectancy. With the results from the Human Genome Project, it has now become feasible to study and characterise the physiological effects of each of these alleles. Deleterious side effects can be identified or ruled out before genetic engineering is ever attempted with such 'type I genes.' In the case of people who carry the HIV resistance gene, for example, medical studies have demonstrated no significant negative impact on health or any physical characteristics. When the likelihood of negative sides effects is shown to be sufficiently low, parents will be able to use type I genetic enhancement to give their child a potentially beneficial allele that other children can receive naturally. Type II genetic enhancements, on the other hand, will not be feasible in the near future because of the possibility of unanticipated side effects.

For the sake of analysis, let us assume that at some point in the future, technical problems associated with genetic engineering of the germline will be eliminated and it will be possible to use the technology safely and efficiently. In practice, this means reaching a point where the risk of birth defects is lower than 4%—the risk encountered in cases of natural conception and gestation. Until this goal is attained, the use of type I genetic engineering will be considered unethical and unacceptable. But if, and when, the risk associated with the technology is reduced below the natural level, we will have to consider the ethics of its use in terms other than safety. And these considerations will be greatly influenced by the political system within which such a discussion takes place.

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All modern democratic societies must balance the opposing aims of individual autonomy and social justice. In the USA, individual autonomy is of paramount importance. If a society allows parents to buy their children advantages, it has no logical basis for banning type I genetic enhancements. Americans would respond to any attempt at a ban with the question, 'Why can't I give my child beneficial genes that other children get naturally?'

In most other Western countries, social justice plays a much larger role. Most European countries try to achieve this by providing equal healthcare and educational opportunities for all children, irrespective of the affluence of their parents. Here, type I genetic enhancements might seem immoral because they are unfair to those children who did not receive them. But there is a flaw in the fairness argument: children are not biologically equivalent to begin with. Everyone is born with advantages or disadvantages across a whole range of physical characteristics as well as innate abilities. Life is not fair.

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In the future, the critical question therefore will be who decides how genetic advantages are distributed. Who decides which child will get the HIV resistance gene, which child will have the potential for a long life-span and which one will have superior protection against cancer and heart disease? Should the decision be left to the randomness of nature, as it is now? Should it be determined by the parents' affluence? Or should it be controlled by the state? There may come a time in the future when an individual or society actually *is* making a decision in favour of randomness when it chooses *not* to make a decision. Alternatively, the desire of a European-style democracy to protect its citizens may lead to an active responsibility of the state to perform type I genetic enhancements, just as childhood vaccination is performed in Europe.

Unfortunately, the provision and regulation of genetic enhancement technology will not be easy. Unlike healthcare, there are almost no limits to genetic enhancements. There can always be greater resistance to diseases, greater longevity, greater physical prowess and greater mental capacity. Furthermore, the innate desire to advantage one's children is so powerful that affluent citizens may buy reprogenetics elsewhere even if their society bans or limits its use—just as Europeans now travel to the USA to purchase human eggs from selected donors.

The use of genetic enhancement could greatly increase the gap between the 'haves' and the 'have-nots' in the world. A gap between classes within societies may emerge initially. But when the cost of reprogenetics drops, as the costs of computers and telecommunications did, it could become affordable to the majority in Western and other industrialised countries. Ultimately, type II genetic enhancements will become feasible too, and then there really will be no limitations. When this happens, the economic and social advantages that wealthy countries maintain could be expanded into a genetic advantage. And the gap between wealthy and poor nations could widen further with each generation until all common heritage disappears. A severed humanity might be the ultimate legacy of unfettered global capitalism.

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The only alternative seems remote today and it may never be viable: a single world state in which all children are provided with the same genetic enhancements and the same opportunities for health, happiness, and success. But politics are far more difficult to predict than science.

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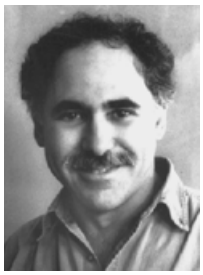

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Vaccine cornucopia

Transgenic vaccines in plants: new hope for global vaccination? • *by Giovanni Levi*

Infectious diseases are still the major threat to life for children and young adults in the third world, causing more than 13 million deaths a year. According to the World Health Organisation, diarrhoeal diseases—such as cholera, dysentery and typhoid fever—alone claim nearly two million lives a year among children under five. Antibiotics to combat these infections exist, but their improper use has largely contributed to the gradual erosion of their efficacy, due to the development of resistance. As David L. Heymann, Executive Director for Communicable Diseases at the WHO pointed out to the US House of Representatives, 'We may only have a decade or two to make optimal use of the medicines presently available', (Heymann, 2000). Also, the price of some antibiotics is still prohibitively expensive for many people in the poorest parts of the world.

If existing treatments fail or are inaccessible, prevention and vaccination become an alternative. It is, therefore, critically important to rapidly develop new strategies of global vaccination. By eradicating smallpox, the WHO has already proven that such a goal can be reached and is now planning to take on polio.

An ideal vaccine for a global vaccination programme should be safe, easy and cheap to produce, temperature stable, and easy to deliver and administer. Effective vaccines against numerous diseases exist, but often do not fulfil all of these demands. A promising alternative could be vaccine production in transgenic plants. European, American and Chinese scientists recently explored the potentials and limits of this technology at a meeting in Erice, Italy, organised by the World Federation of Scientists (http://www.federationofscientists.org/) in collaboration with the European Biotechnology Node for Interaction with China (http://www.ebnic.org/).

Vaccine production in transgenic plants would have several major advantages compared with present technologies. First of all, the cost of production could be reduced by up to three orders of magnitude. For a large-scale production of tomato-based edible vaccines, the cost could be less than one US¢ per dose.